IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,)
)
Plaintiff,)
) C.A. No. 22-228-RGA
v.)
) Trial Volume II
MSN LABORATORIES PRIVATE)
LIMITED, et al.,)
)
Defendants.)

J. Caleb Boggs Courthouse
844 North King Street
Wilmington, Delaware

Tuesday, October 24, 2023
8:29 a.m.
Bench Trial

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: ANTHONY D. RAUCCI, ESQUIRE
BY: JACK B. BLUMENFELD, ESQUIRE

-and-

WILMERHALE
BY: KEVIN S. PRUSSIA, ESQUIRE
BY: LISA J. PIROZZOLO, ESQUIRE
BY: AMY KREIGER WIGMORE, ESQUIRE
BY: JONATHAN A. COX, ESQUIRE
BY: KEVIN M. YURKERWICH, Ph.D.

For the Plaintiff

APPEARANCES CONTINUED:

HEYMAN ENERIO GATTUSO & HIRZEL LLP
BY: DOMINICK GATTUSO, ESQUIRE

-and-

WINSTON & STRAWN LLP
BY: GEORGE LOMBARDI, ESQUIRE
BY: BRYCE COOPER, ESQUIRE
BY: KURT A. MATHAS, ESQUIRE
BY: ELIZABETH GRDEN, ESQUIRE
BY: KEVIN BOYLE, ESQUIRE
BY: BRIAN O'GARA, ESQUIRE

For the Defendants

Also Present:

Dr. Kondal Reddy Bairy

*** PROCEEDINGS ***

08:08:45
08:08:45
08:11:01 DEPUTY CLERK: All rise. Court is now in
08:13:15 session. The Honorable Richard G. Andrews presiding.
08:13:15 THE COURT: All right. Good morning. Please be
08:29:39 seated.
08:29:40 Are we ready to begin or what?
08:29:44 MR. PRUSSIA: We are, Your Honor. We could
08:29:50 either address the issue we discussed last night now or
08:29:52 after Lepore's cross is over.
08:29:56 THE COURT: Well, if it's ready to be discussed
08:29:57 now, you might as well discuss it now and we'll give whoever

needs to be prepare more time to prepare.

MR. PRUSSIA: May I approach, Your Honor, with one piece of paper?

THE COURT: Okay.

MR. PRUSSIA: What is it, Paragraph 140?

Tom, could we put Paragraph 140 of Dr. Steed's reply report on the screen.

So, Your Honor, there's only one issue now on this dispute. This is the paragraph in Dr. Steed's reply report regarding obviousness-type double patenting.

THE COURT: Yeah.

MR. PRUSSIA: And if you look at the line that starts "as I stated previously in my opening report," it's clear to us what he's disclosed is that his opinion is as stated in his opening report. He's limited his obviousness-type double patenting opinions to his opening report.

So based on that disclosure, we think that's the metes and bounds of his opinions that he can offer in this case and so the practical effect of that really reduces down to one issue and that's whether he can offer an opinion with respect to unexpected results. He does not offer an opinion with unexpected results in his opening report, so our position will be that he's not able to do that in the context of this trial.

08:31:06 THE COURT: Well, when you say he didn't offer in his opening report, he didn't offer it in any connection or just in connection with obviousness-type double patenting.

08:31:15 MR. PRUSSIA: In any connection whatsoever. There's no disclosure of opinion with respect to unexpected results in the opening report.

08:31:21 THE COURT: Okay. What do you have to say about that?

08:31:25 MR. MATHAS: Mr. Cooper will address that, Your Honor.

08:31:29 THE COURT: Thank you, Mr. Mathas.

08:31:31 MR. COOPER: Your Honor, I'll give you Dr. Trout's report. So, Dr. --

08:31:40 THE COURT: Are we talking about Dr. Trout or Dr. Steed.

08:31:43 MR. COOPER: Well, so with respect to unexpected results, obviously Exelixis has the burden of production on that. So they address unexpected results in Dr. Trout's rebuttal report. And Dr. Trout identifies --

08:31:56 THE COURT: And by the way, when you say "rebuttal," you mean his second report in the series of three?

08:32:01 MR. COOPER: Right. So it goes Dr. Steed in opening, then Dr. Trout, then Dr. Steed in reply.

08:32:06 And so in Dr. Trout's rebuttal report, Exelixis and Dr. Trout raise unexpected results for the first time, which is, you know, the proper order. We're not - that's what we would expect.

08:32:19 And so Dr. Trout, in his report, identifies objective indicia that support non-obviousness of the inventions and he does that in his section where he is addressing Dr. Steed's 103 obviousness opinions, and he provides that and we can -- I can give you a copy, but I don't think this is in dispute that Dr. Trout addresses it in that section.

08:32:42 And then later on in the report, he has a section on obviousness-type double patenting -- apologies, Your Honor. I wasn't ready to do this right now. I thought we would do it with Dr. Steed.

08:33:02 THE COURT: What you're saying is -- or at least what it sounds like you're saying is, yeah, so Dr. Steed didn't address this, but that's because Dr. Trout didn't address it in the right place?

08:33:13 MR. COOPER: No. Dr. Trout addressed it in the right place, but he addressed it in 103 obviousness. And then when he goes to his obviousness-type double patenting, he only has one page on that and he says -- he doesn't -- he doesn't provide unexpected results for obviousness-type double patenting. He talked about it in his 103 section and

08:33:32 that's exactly what Dr. Steed does in reply. He addresses
08:33:36 objective indicia in the third round, just as you would
08:33:39 expect him to do.

08:33:40 THE COURT: But wait. So, Mr. Prussia, I
08:33:43 thought you said he didn't address unexpected results
08:33:45 anywhere.

08:33:46 MR. COOPER: That's incorrect. He did in his
08:33:48 reply round, just when you would expect us to do so.

08:33:51 MR. PRUSSIA: Your Honor, in his opening report
08:33:52 he did not address unexpected results.

08:33:55 THE COURT: Okay. All right. But he addresses
08:33:57 it in his reply report?

08:33:59 MR. COOPER: Yes. And, of course,
08:34:00 Mr. Prussia --

08:34:00 THE COURT: Okay.

08:34:01 MR. COOPER: -- examined him on his opinions on
08:34:05 that.

08:34:05 THE COURT: And so why isn't that the end of the
08:34:07 matter, he addressed it in his reply report? He doesn't --
08:34:12 there's no -- the normal burden of proof means that the
08:34:20 Defendant is not the one who's addressing it in the opening
08:34:22 round; right?

08:34:24 MR. PRUSSIA: That's right.

08:34:26 Tom, put it back on the screen.

08:34:27 It's just simply a matter of disclosure,

08:34:29 Your Honor. He very clearly says that his opinions are as stated in his opening report. He doesn't make reference to any other opinion that he's provided in his reply report. It's really just a matter of disclosure.

08:34:39 THE COURT: Well, how are you in the least bit prejudiced by this?

08:34:42 MR. PRUSSIA: It's just simply a disclosure matter, Your Honor. I'm not -- I'm not stating or suggesting that they're -- he didn't disclose it in his reply report, but they chose to disclose it this way.

08:34:54 THE COURT: All right. Well, you know, I think it's been disclosed. Maybe the dots are not completed connected, but I think Mr. Prussia has candidly admitted there's no prejudice and so I'm' going to allow it.

08:35:16 MR. COOPER: Thank you, Your Honor.

08:35:17 THE COURT: All right. Leigh, charge that to them.

08:35:23 Okay.

08:35:25 MR. MATHAS: Your Honor, should we bring Dr. Lepore back to the stand?

08:35:28 THE COURT: If you'd like.

08:35:29 MR. MATHAS: Well, he's on cross but that's where we were at.

08:35:32 THE COURT: Yeah, right. I mean, I'm perfectly happy to just sit here if you want, but...

08:35:36 All right. Good morning, Dr. Lepore.
08:35:50 And, Ms. Wigmore.
08:35:53 MS. WIGMORE: Thank you, Your Honor.
08:35:53 CROSS-EXAMINATION (RESUMED)
08:35:53 BY MS. WIGMORE:
08:35:54 Q. Be a good morning, Dr. Lepore.
08:35:55 A. Good morning.
08:35:55 Q. We talked yesterday about your inherency opinion, so
08:35:59 I would now like to move to your opinions on obviousness.
08:36:02 Do you have that in mind?
08:36:03 A. Yes.
08:36:03 Q. Now, it's your opinion that a POSA would have been
08:36:06 motivated and found it obvious to purify by
08:36:09 recrystallization the cabozantinib (L)-malate produced by
08:36:14 the Brown process to prepare API essentially free of the 1-1
08:36:19 impurity; is that right?
08:36:20 A. That's correct.
08:36:23 Q. Now, you testified that a POSA would have been
08:36:26 motivated to monitor and control the 1-1 impurity in the
08:36:30 Brown process; correct?
08:36:31 A. Correct.
08:36:33 MS. WIGMORE: Could we please have DDX Lepore 5?
08:36:33 BY MS. WIGMORE:
08:36:47 Q. This is a slide that you showed during your direct
08:36:51 examination; correct?

08:36:51 A. Correct.
08:36:52 Q. And it says that the 1-1 impurity is a genotoxic impurity; correct?
08:36:57 A. Correct.
08:36:59 Q. Now, to your knowledge, the 1-1 impurity had not been identified as being genotoxic prior to this disclosure of the '349 patent; correct?
08:37:10 A. That's correct.
08:37:13 Q. You testified that quinolines are genotoxic; correct?
08:37:17 A. Correct.
08:37:19 Q. Not all quinolines are genotoxic; correct?
08:37:22 A. That's correct.
08:37:23 Q. Cabozantinib is a quinoline; correct?
08:37:26 A. It has a quinoline moiety, yes.
08:37:33 Q. And cabozantinib is not genotoxic; correct?
08:37:36 A. That's correct.
08:37:38 Q. Now, in your direct examination, you testified about FDA guidelines.
08:37:42 Do you recall that?
08:37:43 A. Yes.
08:37:44 Q. And you testified about a reference called Robinson.
08:37:48 Do you recall that?
08:37:48 A. Yes.
08:37:49 Q. Now, the FDA guidelines do not address cabozantinib specifically; correct?

08:37:54 A. That's correct.
08:37:56 Q. The FDA guidelines do not address the 1-1 impurity;
08:38:00 correct?
08:38:01 A. That's correct.
08:38:02 Q. And the Robinson reference does not address
08:38:05 cabozantinib; correct?
08:38:06 A. That's correct.
08:38:07 Q. The Robinson reference does not address the 1-1
08:38:10 impurity; correct?
08:38:11 A. That's correct.
08:38:14 Q. Do you agree that impurities introduced or created
08:38:18 early in the manufacturing process typically have more
08:38:23 opportunities to be removed in purification operations than
08:38:27 impurities generated late in the manufacturing process?
08:38:29 A. I agree that as a general statement is true, mm-hmm.
08:38:35 Q. And do you agree that those impurities generated
08:38:37 early in the process are less likely to be carried into the
08:38:42 drug substance?
08:38:43 A. In most cases, yes.
08:38:48 Q. Now, I want to focus on your opinion regarding
08:38:51 recrystallization.
08:38:53 There's a purification process at each step of
08:38:56 Scheme 1 in Brown; correct?
08:38:58 A. Yes.
08:39:03 Q. Compounds can be recrystallized in different

08:39:06 conditions; correct?
08:39:07 A. Yes.
08:39:09 Q. And depending on the conditions, a compound may or
08:39:12 may not crystallize -- recrystallize; correct?
08:39:16 A. That's true.
08:39:18 Q. So, turning to what happened in the real world. The
08:39:22 '349 patent discloses a process for making cabozantinib
08:39:27 (L)-malate; correct?
08:39:28 A. Could you repeat that question, please?
08:39:33 Q. The '349 patent discloses a process for making
08:39:38 crystalline (L)-malate -- cabozantinib (L)-malate; correct?
08:39:41 A. That's correct.
08:39:42 Q. And that process has been referred to in this case as
08:39:44 B-2.
08:39:45 Do you recall that?
08:39:46 A. Yes.
08:39:47 Q. You have not given the opinion that the B-2 process
08:39:52 disclosed in the '349 patent was known in the art before the
08:39:56 priority date of the '349 patent; correct?
08:40:00 A. That's correct.
08:40:05 Q. The procedure -- the B-2 procedure from the
08:40:08 '349 patent is different from the A-2 process disclosed in
08:40:13 Brown; correct?
08:40:14 A. So the A-2 process is a name given by Exelixis, but
08:40:23 yes. That's -- that's right. The Brown process is

different from the B-2 process, that's correct. Mm-hmm.

Q. Now, the inventors of the '349 patent did not achieve the purity limitation in Claim 3 by adding a recrystallization step to the Brown process; correct?

A. I need to review that. Can you point to me where I made that statement?

Q. Let me ask it this way: You talked about the B-2 process being disclosed in the '349 patent.

Do you recall that?

A. Mm-hmm.

Q. And you reviewed the B-2 process; correct?

A. Yes. Mm-hmm.

Q. The B-2 process is not simply the Brown process plus a recrystallization step; right?

A. That's correct. Mm-hmm.

Q. Now, let's turn to your opinion regarding the crystalline (L)-malate pharmaceutical composition. Okay?

A. Yes.

Q. You have not given an opinion on whether Brown explicitly teaches pharmaceutical formulation -- pharmaceutical compositions that are essentially free of the 1-1 impurity; correct?

A. Correct.

Q. You have not offered expert opinions on formulation related issues; correct?

08:42:00 A. That's correct.
08:42:02 Q. Now, you testified on direct about two Exelixis documents containing testing on capsules produced from the Regis API.
08:42:13 Do you recall that?
08:42:14 A. Yes. Mm-hmm.
08:42:15 Q. You have not offered an opinion as to whether any cabozantinib (L)-malate capsules were in the prior art; correct?
08:42:26 A. That's correct.
08:42:30 Q. You have not opined on anything having to do with capsules; correct?
08:42:33 A. Correct.
08:42:38 Q. You did not prepare a pharmaceutical composition comprising cabozantinib (L)-malate with a filler, glidant, disintegrant and lubricant; correct?
08:42:48 A. That's correct.
08:42:49 Q. And you did not ask anyone to prepare such a composition as part of this case; correct?
08:42:54 A. That's correct.
08:42:55 Q. You did not do any testing for this case; correct?
08:42:58 A. That's correct.
08:43:01 MS. WIGMORE: Thank you, Dr. Lepore.
08:43:03 No further questions, Your Honor.
08:43:04 THE COURT: All right. Mr. Mathas.

MR. MATHAS: Briefly, Your Honor. Kurt Mathas for MSN.

REDIRECT EXAMINATION

BY MR. MATHAS:

Q. Dr. Lepore, yesterday afternoon you were asked a long series of questions about polymorphic impurity in the context of the Brown reference.

Do you recall that?

A. Yes.

Q. Let's pull up DTX-291 at Page 24 which is Paragraph 97 of Brown, and that's the paragraph that counsel was talking to you about; right?

A. Yes.

Q. And she wanted to talk to you about the word "crystalline form" in the first sentence, do you remember that?

A. Yes.

Q. All right. Now, she didn't show you the last full sentence on this page that says, "The remainder of the crystalline form."

Do you see that sentence?

A. Yes.

Q. And it goes on to say there, "The remainder of the crystalline form of Compound I may comprise other forms of Compound I and/or reaction impurities and/or processing

impurities that arise, for example, when the crystalline form is prepared."

Do you see that?

A. Yes.

Q. And what types of impurities are being discussed there, reaction impurities and process impurities?

Are those polymorphic impurities or chemical impurities?

A. Chemical impurities.

Q. Okay. Now, Claim 3 that we're dealing with in this case and the 1-1 impurity, what kind of impurity is it? Is it a polymorphic impurity, or is it a chemical impurity?

A. It's a chemical impurity.

Q. All right. So, this -- the polymorphic impurity, does that have anything to do with your opinions in this case?

A. No, it doesn't.

Q. All right. Let's talk about some of the things that do matter for the case.

MR. MATHAS: And you can take that down.

BY MR. MATHAS:

Q. I want to talk briefly about your testimony on the Regis batches and that the three Regis batches were inherently free of the 1-1 impurity.

Do you recall that testimony?

A. Yes.
Q. Now, on cross, did counsel confront you with any data or evidence showing test results of Regis batches that were not -- in which -- let me get this straight.
Did counsel show you any evidence or data of Regis batches with 1-1 impurity levels that were over 200 PPMs?
A. No.
Q. Did counsel show you or confront you with any evidence of any Regis capsule batches that showed 1-1 levels over 200 PPMs?
A. No.
Q. And did counsel confront you -- with respect to your opinions on Girindus, did she show you any evidence or data that undermined your opinions that Girindus deviated from the Brown Example 1 process?
A. No.
Q. All right. You were also asked some questions yesterday about a notation in the Exelixis NDA that I want to talk about for a minute.
MR. MATHAS: And to do so, let's pull up PTX-10 at Page 9.
BY MR. MATHAS:
Q. And the paragraph underneath the scheme there, counsel asked you some questions about.

Do you recall that?
A. Yes.
Q. All right. And in counsel's questions -- in connection with her questions about these proposed or potential changes, did she pull out any documents out of the millions of pages that Exelixis has produced in this case and show you any documents where any purported changes existed?
A. No.
Q. Okay. Did she go to any Regis documents and pull out any Regis documents and show you actual information about how a Regis batch purportedly had some form of a change?
A. No.
Q. All right. And so, in -- when you did your analysis of the Regis batches, what did you rely on?
A. I relied on the material that Exelixis provided to the FDA. That's the procedures, and I reviewed those procedures.
Q. Right. And that's -- and is that shown on the next pages of this document that counsel put in front of you?
A. Yes. These are the detailed procedures related to the FDA by Exelixis regarding the Brown process.
Q. And -- okay. And is that the -- we walked through, we put it on the slide, and it was Step 1 and it was Step 2 and everybody was wondering if we were ever going to get

08:47:26 finished, but did you go step by step through the process and compare the words of the Regis process as told to the FDA with the Brown process?

08:47:33 MS. WIGMORE: Your Honor, I object to the leading.

08:47:35 THE WITNESS: Yes, I did.

08:47:36 THE COURT: All right. Well, I'll sustain it.

08:47:38 BY MR. MATHAS:

08:47:38 Q. All right. Dr. Lepore, did you compare the two processes?

08:47:42 A. I did.

08:47:42 Q. And what did you conclude?

08:47:43 A. They are virtually identical.

08:47:48 Q. All right. You were asked some questions yesterday about --

08:47:51 MR. MATHAS: You can take that down.

08:47:51 BY MR. MATHAS:

08:47:53 Q. -- Brown Example 1's use of the word "approximately."

08:47:56 Do you recall that?

08:47:56 A. Yes.

08:47:58 Q. And does Brown's use of the word approximately mean that a POSA would not be able to follow the Brown process?

08:48:05 A. No.

08:48:06 Q. All right. And so a POSA would have still been able to follow the Brown process?

A. Yes.
Q. And, Dr. Lepore, if a person of ordinary skill in the art faithfully followed the Brown Example 1 process, would the POSA have necessarily and inherently obtained cabozantinib (L)-malate that is essentially free of the 1-1 impurity?
MS. WIGMORE: Objection. Leading.
THE COURT: All right. That's what his opinion is so I don't think there's any particular harm. So, I'll overrule the objection.
BY MR. MATHAS:
Q. Dr. Lepore, do you need the question again?
A. Please.
Q. So, if a POSA had faithfully followed the Brown Example 1 process, would the POSA have necessarily and inherently obtained cabozantinib (L)-malate that is essentially free of the 1-1 impurity?
A. Yes.
MR. MATHAS: No further questions, Your Honor.
I do have some exhibits to move in.
THE COURT: All right. Let me just ask: Dr. Lepore, the last question, is it -- is your opinion that faithfully following the process leads to the substance with less than 200 parts per million 1-1, is that based on essentially just the three Regis batches and the various

tests that were done on them?

THE WITNESS: That's correct.

THE COURT: Okay.

Anything further?

MR. MATHAS: I have nothing further, Your Honor.

I do have exhibits to move in.

THE COURT: All right. Let's have them.

MR. MATHAS: All right. Defendants offer DTX-522, DTX-328, DTX-291, DTX-38, DTX-80, DTX-125, PTX-98, DTX-130, DTX-128, PTX-9, DTX-69, PTX-68, DTX-62, DTX-91, DTX-272, DTX-313, DTX-251, and DTX-304.

MS. WIGMORE: No objection.

THE COURT: All right. They're all admitted without objection.

(DTX Exhibit Nos. 38, 62, 69, 80, 91, 125, 128, 130, 251, 272, 291, 304, 313, 328 and 522 were admitted into evidence.)

(PTX Exhibit Nos. 9, 68, and 98 were admitted into evidence.)

THE COURT: Dr. Lepore, you can step down. Watch your step.

MR. MATHAS: And, Your Honor, for our next witness we will call Dr. Maureen Donovan back to the stand to provide her invalidity opinions.

THE COURT: Okay.

Dr. Donovan, you're still sworn from yesterday. Okay?

DIRECT EXAMINATION

BY MR. MATHAS:

Q. All right. Good morning, Dr. Donovan.

A. Good morning.

Q. All right. Let's pick up with your testimony.

Have you prepared some continuation slides to assist in your invalidity testimony here today?

A. Yes, I have.

Q. And we can put on the slide here. Again, we'll follow the numbering scheme from yesterday, DDX picking up with DDX-14.

Now, let's start by looking at the '349 patent again which is JTX-4. And, Dr. Donovan, you testified about this in the context of your infringement opinions. But let's go and look at the related application data which is found on Page 2.

And, Dr. Donovan, what do you understand Exelixis to contend is the priority date for the '349 patent?

A. I've been told they contend that it's February 10th, 2011.

Q. All right. And are you applying that February 2011 date informing your invalidity opinions in this case?

A. Yes, I am.
Q. Okay.
MR. MATHAS: If we can look at the claims of the '349 patent on Page 20 and focus in on Claim 3.
BY MR. MATHAS:
Q. Dr. Donovan, have you reviewed the asserted Claim 3 of the '349 patent for purposes of invalidity?
A. Yes, I have.
Q. All right.
MR. MATHAS: Can we please pull up DDX-15?
BY MR. MATHAS:
Q. Dr. Donovan, what are you showing on DDX-15?
A. This is Claim 3 and then subdivided in some of the major categories, some of which I have addressed previously.
Q. Okay. Now, I notice some highlighting on the left, a color scheme. Tell us what that's going to indicate.
A. The color scheme, again, is the -- is for classifications of excipients, so fillers being indicated by green and disintegrants being indicated by blue, et cetera. So it's just an easy way of keeping track of the categories of excipients.
Q. All right. And if we look at the last limitation, the free of the 1-1 impurity, and go to DDX-16, does the -- does the '349 patent define what essentially free is?
A. Yes, it does. It defines essentially free as less

than 200 parts per million of the 1-1.
Q. And is that what you used in your invalidity opinions?
A. Yes, it is.
Q. All right.
MR. MATHAS: Let's pull up DDX-17, please.
BY MR. MATHAS:
Q. And starting with an overview of the opinions you're going to offer here today, Dr. Donovan, what are you going to be presenting to the Court in this portion of your testimony?
A. So, again, I'm going to provide a little bit of a technical background just to give some context for what we'll be talking about, and then I'll be discussing the process that I used to review Claim 3 and determine that it was obvious.
Q. All right.
MR. MATHAS: Can we go DDX-18, please?
BY MR. MATHAS:
Q. What is the first topic in your technical background that you're going to provide?
A. So, a little bit of a review again about cabozantinib (L)-malate and formulations of cabozantinib (L)-malate.
Q. All right. Dr. Donovan, did the prior art teach cabozantinib (L)-malate and formulations thereof?

A. Yes, it did.

MR. MATHAS: And let's look at the Brown reference again. DTX-291, please.

BY MR. MATHAS:

Q. Dr. Donovan, what is DTX-291?

A. This is a patent application publication. We've been referring to it -- referring to it as Brown.

MR. MATHAS: If we can go to Page 25, Scheme 1.

BY MR. MATHAS:

Q. You've called that up with a box in the lower right-hand corner. What's -- what are you showing here?

A. And this is showing that Brown teaches cabozantinib (L)-malate.

Q. All right. And is this the process that Dr. Lepore discussed yesterday?

A. Yes.

Q. And are you relying on Dr. Lepore's testimony in forming your opinions in this case?

A. Yes, I am.

Q. All right. Dr. Donovan, does Brown contain any discussion of how its compounds are formulated?

A. It does describe pharmaceutical compositions, yes.

Q. Okay.

MR. MATHAS: Let's look at Page 22 of Brown, paragraph 87.

08:55:47 BY MR. MATHAS:
08:55:47 Q. Dr. Donovan, what is paragraph 87 of Brown discussing?
08:55:51 A. Well, it's discussing pharmaceutical compositions. It's calling out solid dosage forms being preferred. It's identifying those solid dosage forms for oral administration. It's identifying capsules and tablets among some other dosage forms. And identifying those as being particularly preferred.
08:56:08 And in Brown, they're suggesting the use of at least one pharmaceutically acceptable excipient.
08:56:14 Q. All right. Let's turn and talk about excipients now.
08:56:16 MR. MATHAS: And go to DDX-19.
08:56:16 BY MR. MATHAS:
08:56:21 Q. So, the -- the next topic here is on the -- the claimed excipient limitations. Does Brown describe the use of these excipients?
08:56:29 A. Yes, Brown does.
08:56:30 Q. All right.
08:56:31 MR. MATHAS: Let's go back to Brown, which is DTX-291, Page 21, paragraph 82.
08:56:37 Q. What does Brown describe here?
08:56:39 A. Brown, again, is starting to describe the pharmaceutical compositions and their preparation. And Brown directs the reader to Remington's Pharmaceutical

Sciences, a text that we've already talked about, and suggests that there's information in Remington's that a POSA could use to prepare those pharmaceutical compositions, and describes solid dosage forms of Compound I being mixed with at least one pharmaceutically acceptable excipient.

Q. Okay.

MR. MATHAS: Let's look at the second half of that paragraph.

BY MR. MATHAS:

Q. Dr. Donovan, what are some of the excipients that Brown, in paragraph 82, says can be used in the solid oral dosage forms of cabozantinib?

A. So Brown, again, identifies a number of different categories of excipients, and I've highlighted here the ones that are of discussion. Fillers, disintegrating agents, lubricants. And, again, the -- in the lubricant discussion, they've included talc, which is a well-known glidant.

Q. All right. We'll come back to that in a minute, but on the last slide we had saw reference to Remington's. Do you recall that?

A. Yes.

Q. And that reference to Remington's is -- is here in paragraph 82 of Brown. So, I want to take a look at Remington's for a moment.

MR. MATHAS: And to do so, let's pull up

08:57:52 DTX-284, please.

08:57:52 BY MR. MATHAS:

08:57:56 Q. Dr. Donovan, what is DTX-284?

08:57:58 A. This is the 20th edition of Remington's Science and Practice of Pharmacy.

08:58:04 Q. And is this the edition that was cited in paragraph 82 of Brown?

08:58:07 A. No, they cited the 18th edition. But they're quite similar. Most of the information carries from one edition to the next.

08:58:15 Q. All right. Are you aware of any meaningful differences between the 18th and 20th editions for purposes of your opinions?

08:58:20 A. Not in the sections I reviewed for this case.

08:58:22 Q. All right.

08:58:23 MR. MATHAS: Let's turn to Chapter 45 of DTX-284, the Remington's reference.

08:58:27 BY MR. MATHAS:

08:58:32 Q. And so that's on DTX-284 at Page 4.

08:58:35 What particular chapter are you calling out here?

08:58:38 A. So this is the chapter in Remington's that's describing oral solid dosage forms.

08:58:43 Q. All right. And looking at the -- the first sentence here in that chapter, what does Remington's disclose?

A. The first sentence just starts out saying that drug substances are frequently administered orally, and they -- identifies the use of tablets and capsules.

Q. Is there a section in Remington's that discusses what ingredients can be used in tablets?

A. Yes, there is a section in this chapter.

MR. MATHAS: Let's turn to Page 6 of the exhibit, section on tablet ingredients.

BY MR. MATHAS:

Q. What does Remington's disclose here?

A. So, again, they just -- they're describing that the active or therapeutic ingredient for the tablet is often combined with other, what they are referring to as, inert materials or excipients or additives, kind of interchangeable terms at times.

And then they go on to describe what those other types of excipients would be by classification. And, again, they -- they identify various classifications of excipients, including diluents, glidants, lubricants, and disintegrants.

Q. All right.

MR. MATHAS: Can we please pull up DDX-20.

BY MR. MATHAS:

Q. What are you showing on this slide, Dr. Donovan?

A. So, in -- further into the chapter, they actually have some sections about each of these excipient categories.

08:59:58 And so what I've done is -- is highlight the beginning portions, or the complete portions, depending on each of those sections.

09:00:05 Q. All right.

09:00:06 MR. MATHAS: Let's take a closer look at the glidant section, which is found on Page 8 of DTX-284.

09:00:07 BY MR. MATHAS:

09:00:13 Q. What does -- what does the glidant section disclose?

09:00:17 A. The glidant section, again, describes the typical definition for glidants, and then gives a couple of examples of glidants; one being colloidal silicon dioxide, the other being talc. And we've discussed talc earlier so that's highlighted here.

09:00:32 Q. And so -- and as of February 2011, would a POSA have understood that talc could be used as glidant?

09:00:37 A. Yes, they would.

09:00:39 Q. All right. Were there other textbooks available to the persons of skill in art -- in the art discussing tablet formulations as of February 2011?

09:00:49 A. Yes, there were.

09:00:50 MR. MATHAS: Let's pull up DTX-288.

09:00:50 YB MR. MATHAS:

09:00:54 Q. Dr. Donovan, what is DTX-288?

09:00:56 A. This is a text called "Pharmaceutical Dosage Forms: Tablets, Volume I." There's multiple volumes, even just

describing tablets. It's in a volume series of other dosage forms.

Q. All right.

MR. MATHAS: Let's go to Chapter 2 of Lachman at page -- DTX-288 at 95.

BY MR. MATHAS:

Q. What is Chapter 2 of Lachman covering?

A. Chapter 2 is describing tablet formulations and design.

MR. MATHAS: Let's go within Chapter 2 to Page 113.

BY MR. MATHAS:

Q. Dr. Donovan, what is Lachman describing on Page 113 about tablets?

A. So, similar to what we saw in Remington, descriptions of excipients that are used in tablets. And Lachman divides those into subcategories based on their functionality. And so the first category, things -- the kinds of excipients that are used to contribute to the tablet formation process; so, diluents, binders, lubricants, glidants. So diluents, lubricants, and glidants that we've been talking about.

And then in a separate category, some of the excipients that we use to -- to induce particular performance categories or optimize particular performance characteristics of the tablet. And so that's where Lachman

decided to include disintegrants. Among others.
Q. Okay. Does Lachman have sections in his chapter on each of the various categories of excipients?
A. Yes, he does.
MR. MATHAS: Let's go to DDX-21, please.
BY MR. MATHAS:
Q. What are you showing here?
A. Again, similarly, the beginning portions or the full portion of the sections in Lachman describing those four excipient categories.
Q. All right.
MR. MATHAS: Let's go forward to Chapter 3 of Lachman, which we find on DTX-288 at 151.
BY MR. MATHAS:
Q. What is Chapter 3 covering?
A. Chapter 3 is covering compressed tablets using -- or by wet granulation.
Q. And does this chapter in Lachman have a section on excipients that are used in wet granulation?
A. Yes, it does.
MR. MATHAS: Can we pull up Page 171 of the exhibit, please?
BY MR. MATHAS:
Q. What is this section, Dr. Donovan?
A. This section, again, is talking about excipients used

in tablets formed via wet granulation and it's identifying excipients and identifies fillers, disintegrants, lubricants, and glidants as excipients that would be used.

Q. Okay. Does Lachman provide any exemplary formulations in its Chapter 3?

A. Yes, there are a number of exemplary formulations in the chapter.

Q. All right.

MR. MATHAS: Let's look at some of those, starting with Example 6, which spans the document Pages 176 to 177.

BY MR. MATHAS:

Q. What are you showing here Dr. Donovan?

A. So this is one of the examples in this chapter, and the reason I like this example is that it doesn't -- it's not an example for a specific drug. It teaches a POSA that this formulation would likely be suitable as a starting formulation for many drug substances. And so, it tells us about the use of a drug.

And then I'll go back to the beginning section, where there's a little bit of instruction or information about the design and the formulation. And it identifies the use of a filler, in green. And then highlighted in green, the substances.

In the example, the use of a disintegrant, the

use of a lubricant, and, if necessary, the use of a glidant. And each of those, a filler, a disintegrant, a lubricant, and a glidant are included in this prototype formulation.

Q. All right. And how would a POSA, as of February of 2011, have used a drug-agnostic prototype formulation like this?

A. Well, if they were -- if they were attempting a -- a formulation of a drug substance, they would look at this example and they might choose to use exactly this as a starting point to develop a tablet. And they may need to further optimize, they may need to switch out excipients for something else in the same category if, during an excipient compatibility study, something demonstrates that they could choose or should choose a different excipient. But this is an excellent starting composition.

Q. And would changing out those excipients, as you mentioned, would that be routine?

A. Yes. Exactly. That's what -- that's what formulators do.

Q. Okay.

MR. MATHAS: Let's look at another example, Example 16, which is found on Page 188 of Exhibit 288.

BY MR. MATHAS:

Q. What are you showing in Example 16?

A. So this is another example of one of the

drug-agnostic formulations that's in the chapter. Again, many drugs would be expected to be suitable and -- and be able to be used with this formulation. The formulation describes the choice of a number of different types of fillers and gives a different combination of disintegrant, lubricant, and lubricant -- and glidant in the formulation.

Q. Okay. Now, we've heard over the course of the trial that cabozantinib is a tyrosine kinase inhibitor; is that right?

A. That's right.

Q. Okay. And did you look at any references related to formulating tyrosine kinase inhibitors?

A. I did.

MR. MATHAS: Can we pull up DTX-335, please.

BY MR. MATHAS:

Q. What is DTX-335?

A. This is a patent application publication. And it's describing tyrosine kinase inhibitors. Describing combinations, as indicated in the abstract. And I'm going to refer to this as the '081.

Q. Okay. Let's go -- does DTX-335 describe whether the compounds can be formulated into dosage forms?

A. Yes, it does.

MR. MATHAS: Okay. Let's go forward to paragraph 102 of the '081 application. DTX-335 at Page 14.

BY MR. MATHAS:
Q. What's being disclosed in paragraph 102?
A. So, here they're talking, again, about the pharmaceutical compositions for kinase inhibitors and they're described as suitable oral dosage forms, including but are not limited to tablets and capsules, and then they go and describe the components of those compositions; may contain more -- they may contain excipients and those excipients would include fillers, disintegrants, lubricants, glidants, other categories potentially.
Q. And does the '081 application provide further descriptions of these exhibit categories --
A. Yes, it does.
Q. -- excipient categories?
A. Yes, it does.
MR. MATHAS: Let's take a look at the next page, paragraphs 104 to 107.
BY MR. MATHAS:
Q. What are you showing here, Dr. Donovan?
A. Again, similar to the other resources, the sections that are included here are the sections in the '081 describing glidants, describing disintegrants, describing lubricants and describe glidants [sic].
MR. MATHAS: All right. Let's focus in on the glidant paragraph, paragraph 107, if we could.

BY MR. MATHAS:
Q. What does paragraph 107 show, Dr. Donovan?
A. They're identifying suitable glidants for use, colloidal silicon dioxide and talc.
MR. MATHAS: All right. Can we go to DDX-22, please.
BY MR. MATHAS:
Q. And we'll turn and we'll talk about the last issue in your technical background, Dr. Donovan.
What is that?
A. I'm going to talk about limiting the impurities that -- that may occur during formulation.
Q. And did the prior art teach a formulator about limiting impurities during formulation development?
A. Yes, it did.
MR. MATHAS: Let's take a look at DTX-328.
BY MR. MATHAS:
Q. What is DTX-328?
A. This is the Robinson article that we've talked about before, but it's an article talking about control of genotoxic impurities in APIs.
Q. All right. And does Robinson describe limiting impurities in drug products?
A. Yes. Yes, Robinson does.
MR. MATHAS: Okay. Can we go to the Robinson's

introduction on Page 1 and pull that up?

BY MR. MATHAS:

Q. What are you highlighting from the introduction of Robinson?

A. Well, Robinson starts with the -- the directive essentially that ensures safety of pharmaceutical products is a responsibility of chemists, engineers, formulators involved in their manufacture. So, there are a number of individuals that are touchpoints to, again, ensure that the pharmaceutical product is safe and in the context of this article it's about genotoxic impurities.

Q. Okay. And Dr. Lepore testified earlier from the perspective of a chemist; is that correct?

A. That's correct, yes.

Q. And now you are testifying from the perspective of a formulator; is that right?

A. Yes.

Q. Okay. All right. Now, would a POSA have been aware of any other teachings in the prior art about limiting impurities in dosage forms?

A. Yes.

MR. MATHAS: Let's take a look back at Lachman's, which is DTX-288, Page 63 of the reference at the section entitled "Stability."

BY MR. MATHAS:

Q. What does Lachman teach us about these issues?

A. So Lachman's teaching us that when we're designing a solid dosage form, tablets and capsules for example, that we need to identify the excipients that we're going to be using and how to put them together, obviously, for the composition. But it's important to know that no toxic substances are formed from those combinations.

MR. MATHAS: Okay. Let's look at the next section in Lachman's on pages 98 and 99.

BY MR. MATHAS:

Q. What does Lachman describe here?

A. Similarly, the Lachman is describing that in -- when formulating one of the most important activities in the preformulation activities is a drug excipient compatibility study. So as we're selecting the components to include with our API, that we demonstrate using routine experimentation really, the combination -- that combinations of the excipients that we're going to use do not cause -- do not cause additional materials to form or impurities to -- to form within the dosage form or at least in limited amounts.

MR. MATHAS: Okay. Let's take a look at another guidance, DTX-325.

BY MR. MATHAS:

Q. What is DTX-325?

A. This is Remington's, also, in -- now in a second

volume of Remington.

MR. MATHAS: All right. If we go forward to Page 14, near the section titled "Chemical Properties."

BY MR. MATHAS:

Q. What does Remington discuss here?

A. Okay. And what Remington is also discussing there, this is within a discussion of preformulation activities, that physical and chemical stability is important to maintain in the pharmaceutical product and it's imperative that during preformulation that those characteristics are evaluated. And again, the -- sort of a similar statement, evaluation of physical and chemical stability of a new drug substance is important during preformulation.

Q. Dr. Donovan, are there any regulatory guidance documents regarding limiting impurities in drug products?

A. Yes. There's quite a few of them.

MR. MATHAS: Let's go to DDX-23, please.

BY MR. MATHAS:

Q. What are you showing here, Dr. Donovan?

A. So, again, I'm showing even a subset of the regulatory guidance documents regarding impurities in pharmaceutical products and pharmaceutical systems. And what I've got pulled up to the front at least are the -- certainly the genotoxic impurity guidance, which is -- which is important for this case.

And then another guidance that speaks to impurities, the impurities in new drug products, and there's other similar guidances that contain instructions to formulator in the industry about how -- about how to identify -- how to quantify impurities that are -- that -- that are in the formulations or in the API.
Q. Okay. And we'll look at some of those in more detail later.
MR. MATHAS: But let's go to DDX-18 at this point -- I'm sorry. DDX-24 at this point.
BY MR. MATHAS:
Q. And what's the next topic that we'll be discussing?
A. So I'm actually going to be discussing the process I went through to evaluate Claim 3 in terms of obviousness -- obviousness and my determination that Claim 3 is obvious.
Q. Okay. And in reaching that opinion, Dr. Donovan, did you apply your understanding of the applicable legal standard for obviousness?
A. Yes, I did.
MR. MATHAS: Let's go to DDX-25, please.
BY MR. MATHAS:
Q. Dr. Donovan, is this the legal standard for obviousness that you applied in reaching your invalidity opinions in this case?
A. Yes, it is.

Q. All right. And so, did you work through the four steps shown here on -- in the bullets?
A. Yes, I did.
Q. All right. Let's -- let's do that now. Let's go through them one by one.
The first point on the level of ordinary skill in the pertinent art.
MR. MATHAS: Can we please pull up DDX-26.
BY MR. MATHAS:
Q. Dr. Donovan, what are you showing on the left-hand side of DDX-26?
A. I'm showing my definition of a POSA in this matter and that was read into the record yesterday, I think. And then it's in comparison to Dr. Myerson's position or definition of a POSA.
And they're -- they're rather similar. They're different in education potentially or experience, but they're relatively the same.
Q. All right. Would any of your invalidity opinions change if considered from the perspective that Exelixis has set out for a person of ordinary skill?
A. No.
MR. MATHAS: Okay. Let's turn next to DDX-27, please, and talk about the second element in the obviousness analysis, the scope and contents of the prior art.

BY MR. MATHAS:
Q. Dr. Donovan, as part of your obviousness analysis, did you determine the scope and content of the prior art?
A. I did. And before the priority date there was a significant amount of art about pharmaceutical compositions and what I've highlighted here is, as I've already discussed, the four pieces that are shown in the foreground, those are primarily going to be the ones I'm talking about this morning.
Q. Okay. Now as -- Dr. Donovan, at the third step of the obviousness analysis, did you ascertain the differences, if any, between the claimed invention and the prior art?
A. Yes, I did.
Q. All right. And did you do that by comparing what is recited in Claim 3 with what was disclosed in the prior art references?
A. Yes, I did.
MR. MATHAS: All right. Let's take a look, again, at the claim in DDX-28. And let's look --
BY MR. MATHAS:
Q. Let's start by talking about the compound element of the claim.
A. Mm-hmm.
Q. Dr. Donovan, does the prior art disclose the cabozantinib (L)-malate compound that is recited in Claim 3

of the '349 patent?
A. Yes, it does. I've discussed previously that Brown discloses cabozantinib (L)-malate.
Q. All right. Let's check that off real quick.
MR. MATHAS: If we go to 291, 25. We've seen this before.
BY MR. MATHAS:
Q. What are you showing, Dr. Donovan?
A. I'm showing Brown. And the structure in the red box on the bottom right is cabozantinib (L)-malate.
Q. So Brown discloses cabozantinib (L)-malate compound recited in Claim 3?
A. Yes.
MR. MATHAS: Okay. Let's go to the next slide, DDX-29.
BY MR. MATHAS:
Q. And you've highlighted in red here two -- two additional claim elements. And taking these elements, Dr. Donovan, does the prior art disclose tablet and capsule pharmaceutical compositions for oral administration?
A. Yes. Brown discloses compositions and also discloses tablets and capsules as compositions.
Q. Okay. Does Brown also disclose oral administration?
A. Yes, Brown does.
MR. MATHAS: All right. Let's look back at

09:16:55 DTX-291, Page 22, paragraph 87 of Brown.
09:16:55 BY MR. MATHAS:
09:16:59 Q. What are you showing here?
09:17:00 A. Again, we're just -- this is what I discussed
09:17:03 previously, this is the excerpt out of Brown where they're
09:17:05 beginning to describe pharmaceutical compositions,
09:17:08 identifying oral administration for those compositions,
09:17:13 tablets and capsules being particularly preferred.
09:17:17 Q. All right.
09:17:17 MR. MATHAS: Let's go to the claims of Brown,
09:17:18 DTX-291, 41 and 42.
09:17:18 BY MR. MATHAS:
09:17:21 Q. Does Brown also claim pharmaceutical compositions of
09:17:25 cabozantinib (L)-malate?
09:17:26 A. Yes. Brown does. So I'm going to -- Claim 11
09:17:29 describes a pharmaceutical composition containing
09:17:32 cabozantinib (L)-malate, the chemical name shown there. And
09:17:36 then in -- and pharmaceutical -- with pharmaceutically
09:17:39 acceptable excipients, and I've also included Claim 4 as a
09:17:43 basis that that is cabozantinib (L)-malate.
09:17:47 Q. So does Brown disclose that cabozantinib (L)-malate
09:17:50 can be formulated as a tablet or capsule composition for
09:17:54 oral administration as recited in Claim 3?
09:17:56 A. Yes.
09:17:57 Q. All right.

09:17:57 MR. MATHAS: Let's pull up DDX-30, please, and look at the next limitation highlighted here which is the excipient limitation.

09:18:04 BY MR. MATHAS:

09:18:06 Q. Does the prior art disclose, Dr. Donovan, the use of the claimed excipients?

09:18:11 A. Yes. Lots of prior art disclosed those -- use of those excipients. Brown, Lachman and the 081 in particular that I've discussed describe the use of those excipient types.

09:18:25 Q. All right.

09:18:26 MR. MATHAS: Let's look at Brown Paragraph 82, again, DTX-291 at 21.

09:18:28 BY MR. MATHAS:

09:18:31 Q. What does Brown teach here about any significance?

09:18:35 A. Brown teaches that for a pharmaceutical composition, the use of fillers, disintegrating agents, lubricants and then talc -- as we've discussed, talc is a glidant and is recognized as a glidant -- those would be appropriate for use in those compositions.

09:18:49 Q. All right.

09:18:50 MR. MATHAS: Let's look at Lachman Example 6, again, DTX-288 at 176.

09:18:52 BY MR. MATHAS:

09:18:55 Q. What does Lachman disclose with respect to the

claimed excipients?
A. Lachman discloses a prototype formulation that contains those exact four categories of excipients. So, fillers, disintegrants, lubricants and glidants.
MR. MATHAS: And let's look at the 081 application publication, DTX-335 at 14.
BY MR. MATHAS:
Q. What does it disclose with respect to the claimed excipients?
A. And the 081, again, disclosing oral dosage forms that are tablets and capsules using fillers, disintegrants, lubricants and glidants as excipients.
Q. Dr. Donovan, in your opinion, would the person of ordinary skill in the art have been motivated to combine the teachings of the prior art references that we've been looking at to formulate cabozantinib (L)-malate into a tablet or capsule composition with the claimed excipients?
A. Yes, they would.
Q. And why is that?
A. Well, again, they have -- with cabozantinib (L)-malate as an API, trying to provide a convenient method for that to be administered. Pharmaceutical composition that's a tablet or a capsule is well known. And the excipient combinations that are described are also well known in the art for making those compositions.

Q. All right. And did the three references that we've just looked at Brown and Lachman and the 081 publication application, would those have motivated the POSA?
A. Yes, certainly. Brown in particular has -- has all of the components, again, with the proviso that talc is known as a glidant. And if one was uncertain, it could easily look at Lachman for a descriptive prototype formulation containing those four excipients.
Q. All right. And how would the 081 application factor in?
A. The '081, again, further supports in this time specifically for tyrosine kinase inhibitors, the same formulation would be appropriate.
Q. All right. In your opinion, Dr. Donovan, would the person of ordinary skill in the art as of February of 2011 have had a reasonable expectation of success in formulating a cabozantinib (L)-malate tablet or capsule composition with the claimed excipients?
A. Yes, they would.
Q. And, again, why is that?
A. Well, again, they -- these excipients are well known. There are a number of different grades of materials and a number of different materials in each of those categories. So, if there was the need to -- even if one started with the Lachman example and needed to change one of those excipients

to something else in the category for whatever desired purpose, it would be possible. Looking at the structure of cabozantinib (L)-malate, just as the chemical structure, formulators oftentimes do that, looking for chemical indicators just in the structure that they might need to be concerned with. I couldn't identify any structures that I thought were concerning regarding general formulation of cabozantinib and so, perfectly motivated to combine those materials and be -- I would have a reasonable expectation that I would have a successful pharmaceutical composition.

Q. All right. And when you say "I" there, are you referring to the person of ordinary skill in the art?

A. Yes.

Q. As of February 2011?

A. Also would do that.

Q. All right.

MR. MATHAS: Let's go to DDX-31, please, and turn and talk about the last limitation of the claims.

BY MR. MATHAS:

Q. Dr. Donovan, does the prior art disclose cabozantinib (L)-malate that is essentially free of the 1-1 impurity?

A. Yes, it does.

Q. All right. And did Dr. Lepore testify about that during his testimony?

A. Yes, he did. And described how Brown discloses

09:22:44 essentially cabozantinib (L)-malate essentially free of the 1-1 impurity.
09:22:48 Q. And that testimony was related to the cabozantinib API; right?
09:22:51 A. Yes.
09:22:52 Q. And the claim here is talking about the pharmaceutical composition containing that API being essentially free; is that right?
09:23:00 A. That's right.
09:23:01 Q. Now, did the prior art include teachings about the about formulating drug compositions to limit impurities?
09:23:08 A. Yes, the prior art did. I showed some examples. It's well -- it's well known, and it's a tenet of formulation to minimize or to be concerned with stability, to be aware of stability of the API in other -- other components in the composition.
09:23:26 Q. Okay.
09:23:27 MR. MATHAS: Let's look back at Lachman 288 at Page 63.
09:23:29 BY MR. MATHAS:
09:23:31 Q. And, again, what would a Lachman have taught the formulator about formulating an API into a dosage form with respect to impurities?
09:23:42 A. So, again, highlighting that the formulator needs to know about the inherent stability, needs to understand the

excipients that are being used and that when combined with the API that no toxic substances are formed.

Q. And would this concept have been well known to a formulator as of February 2011?

A. Very well known, yes.

Q. And in your opinion, as of February 2011, would a formulator have been motivated to monitor for the 1-1 impurity?

A. Yes, they would.

Q. And why is that?

A. Because the formulator would have learned from the chemists involved just knowing that there -- there are indicators that -- that there may be impurities or carry-through substances that might be toxic that -- that monitoring the 1-1 would be something to do during formulation development.

Q. Okay. In your opinion, Dr. Donovan, would the person of ordinary skill in the art have been motivated to use the cabozantinib (L)-malate API that is essentially free of the 1-1 impurity from the Brown reference to formulate that into a pharmaceutical composition that was essentially free of the 1-1 impurity?

A. Yes, they would.

Q. And why is that?

A. Well, again, the Brown -- the Brown publication

09:25:01 essentially describes that. A pharmaceutical composition, the API that Brown is describing is free of the 1-1 -- or essentially free of the 1-1 impurity, and the Brown reference describes compositions with the -- with the four categories of excipients and others -- other information in the art about the excipients certainly supports that.

09:25:21 Q. All right. Dr. Donovan, would a -- in your opinion, would a person of ordinary skill in the art --

09:25:29 MR. MATHAS: You can take that down.

09:25:29 BY MR. MATHAS:

09:25:30 Q. Would a person of ordinary skill in the art have had a reasonable expectation of success in formulating a pharmaceutical composition of cabozantinib (L)-malate that is essentially free of the 1-1 impurity?

09:25:40 A. Yes, basically starting with the cabozantinib (L)-malate of the Brown process understand -- looking at that molecule, a POSA would have reasonable expectation of success of developing a pharmaceutical composition of cabozantinib (L)-malate as described in Claim 3.

09:26:01 Q. And so, the POSA would have a reasonable expectation of success of formulating that cabozantinib (L)-malate into a composition that was essentially free of the 1-1 impurity?

09:26:10 A. Yes.

09:26:12 Q. Okay. Let's turn briefly -- Dr. Donovan, as part of your analysis, did you also consider objective indicia of

09:26:19 non-obviousness?
09:26:20 A. I did.
09:26:21 MR. MATHAS: Let's turn to DDX-32, please, and start with unexpected results.
09:26:26 BY MR. MATHAS:
09:26:28 Q. Dr. Donovan, what is your understanding of the unexpected results that are alleged here?
09:26:32 A. Well, I've come to understand that the -- there's a -- the formation of a cabozantinib capsule or the -- yeah, the formulation of a cabozantinib capsule was -- was determined to be unexpected by the inventors. The ability to use wet granulation to develop a tablet was -- was stated as being unexpected by the inventors. And the ability to have that composition have storage stability was unexpected to them.
09:27:04 Q. Let's talk about those alleged claims of unexpectedness, and we'll start with the capsule claim.
09:27:14 Now, would a person of ordinary skill in the art have expected to be able to formulate cabozantinib (L)-malate into a capsule that was essentially free of the 1-1 impurity?
09:27:24 A. Yes, they would. Starting with the cabozantinib (L)-malate that's essentially free of the 1-1 impurity combining with known excipients and known manners especially with the capsule. Oftentimes, we can just simply premix the

components and put them into capsule shell.
Q. All right. And are you aware of any evidence that supports that the cabozantinib (L)-malate from the Brown Example 1 process could be used in capsules that are essentially free of the 1-1?
A. I've heard about capsules that were formulated from the Regis batches that were -- would have been essentially free of the 1-1.
Q. And that was during Dr. Lepore's testimony?
A. Yes.
Q. All right. And so, let's talk about the second point here. Would a person of ordinary skill in the art have expected to be able to formulate a cabozantinib tablet that was essentially free of the 1-1 impurity using wet granulation?
A. Yes. Starting with a API essentially free of the 1-1 there -- a POSA would understand that using a wet granulation process would likely maintain the essentially free status of that 1-1 impurity.
Q. Okay. Does the '349 patent Claim 3 allow for the use of tablets formulated by wet granulation?
A. It allows for the use of tablets made by any method.
Q. Okay. Does the '349 patent, the specification, describe any specific or particular ways of formulating the claimed composition such that it limits the 1-1 impurity?

A. No, it does not.

MR. MATHAS: Let's look at what the specification does disclose. That's JTX-4, Page 13, Columns -- sorry, Column 20, Lines 36 to 52, Section 3 on pharmaceutical compositions.

BY MR. MATHAS:

Q. What does the patent describe about how to make the claimed formulations, Dr. Donovan?

A. Well, the patent is -- is directing individuals to use techniques already known for the -- for the preparation and production of those unit dosage forms and guides the reader to Remington or to Swarbrick, which we've talked about.

Q. Okay.

MR. MATHAS: Can we go forward to the next column, Column 21, Lines 37 to 45.

BY MR. MATHAS:

Q. Now, with respect to formulating compositions of the invention, what does the '349 patent describe about how a -- that can be done?

A. Again, similarly, pointing to using methods known to the skilled artisan, these compositions can be easily formulated.

Q. All right. Dr. Donovan, in your opinion, was there anything unexpected about formulating a tablet or a capsule

to be essentially free of the 1-1 impurity?
A. No, there wasn't.
Q. Now, in your opinion, was there anything novel about using the claimed excipients in a formulation to formulate a tablet or capsule that's essentially free of the 1-1 impurity?
A. No. Those are extremely commonly used categories of excipients.
Q. All right. The last point you mentioned on unexpected results was something about stability over shelf life; is that right?
A. Yes.
Q. Now, with respect to that claim, Doctor, the alleged secondary consideration related to shelf life, does asserted Claim 3 of the '349 patent require any particular stability over any particular shelf life?
A. No, it doesn't.
MR. MATHAS: Let's go to DDX-33, please. And turn and talk about the next issue here, blocking patents.
BY MR. MATHAS:
Q. Generally, Dr. Donovan, what's your understanding of a blocking patent?
A. Well, my understanding is if there's a patent that's -- that's been issued, and it has -- its claimed materials will limit the -- the ability and/or the

09:31:33 motivation to work in similar areas, because one couldn't commercialize anything that one had worked on because there was already a preceding patent.

09:31:43 Q. Okay. And did that type of blocking patent deterrence exist here?

09:31:50 A. Yes, it did.

09:31:51 MR. MATHAS: Let's pull up DTX-192, please.

09:31:51 BY MR. MATHAS:

09:31:54 Q. What is DTX-192, Dr. Donovan?

09:31:56 A. This is an international patent publication dated in 2005. And it describes cabozantinib and pharmaceutically related salts.

09:32:06 Q. Okay.

09:32:07 MR. MATHAS: Let's then next pull up DTX-13, please.

09:32:11 BY MR. MATHAS:

09:32:13 Q. What is DTX-13, Dr. Donovan?

09:32:16 A. Again, this is U.S. Patent '473, also describing cabozantinib and cabozantinib salts.

09:32:22 Q. And when did it issue, Dr. Donovan?

09:32:24 A. 2009.

09:32:25 Q. All right. In your opinion, would the existence of the '140 publication and '473 patent have deterred individuals in the field from pursuing cabozantinib formulations like those claimed in the '349 patent?

A. Yes, it would.
Q. Okay.
MR. MATHAS: Let's go to DDX-34, please. Next point on nexus.
BY MR. MATHAS:
Q. Again, very generally, what does nexus refer to, Dr. Donovan, in your understanding?
A. Well, my understanding is nexus tells us that the claims of the patent need to be directly related to the commercial success of the embodiment of those claims.
Q. Okay. And in your opinion, Dr. Donovan, could an equally viable formulation of cabozantinib (L)-malate be prepared that is not covered by asserted Claim 3 of the '349 patent?
A. Yes, it could. And even the MSN formulation demonstrates that.
Q. All right. And that's based on your infringement testimony from yesterday?
A. Yes; that is doesn't contain a glidant.
Q. Okay. All right.
MR. MATHAS: Now, let's go to DDX-35, please.
BY MR. MATHAS:
Q. And you've highlighted some other secondary considerations here. Did you consider the other objective indicia listed in reaching your opinions in this case,

Dr. Donovan?
A. I did consider them, and I rely on the expertise and the opinions of Dr. Mega and Dr. McDuff for those.
Q. Very good. And we'll here from Dr. Mega and Dr. McDuff tomorrow.
Finally, Dr. Donovan --
MR. MATHAS: Let's go to DDX-36, please.
BY MR. MATHAS:
Q. And now that we've been through your analysis, your obviousness analysis, your obviousness opinions, Dr. Donovan, can you please summarize your obviousness opinion for the Court?
A. My opinion is that Claim 3 is invalid as being obvious.
Q. For the reasons you've discussed during this testimony?
A. Yes.
MR. MATHAS: Thank you, Your Honor. I have no further questions at this time.
THE COURT: All right. Cross-examination.
MS. PIROZZOLO: Thank you, Your Honor.

CROSS-EXAMINATION

BY MS. PIROZZOLO:
Q. Good morning, Dr. Donovan.
A. Good morning.

Q. I'd like to start by talking about the '349 patent, okay?
A. Yes.
Q. The specification of the '349 patent teaches that the 1-1 impurity should be minimized in pharmaceutical compositions for human administration; correct?
A. Can you point me to a paragraph in the '349 about that?
Q. Sure.
MS. PIROZZOLO: If we pull up Joint Exhibit 4, this is Tab 5 in the second volume. And if we go to Column 22, Lines 8 through 27.
BY MS. PIROZZOLO:
Q. We have it up on the screen.
A. Okay.
Q. The figure, that is the 1-1 impurity; correct?
A. That's what I've been -- that's what I know as the 1-1 impurity, yes.
Q. Okay. And the patent refers to "minimizing the concentration of contaminants or byproducts, such as the 1-1 impurity in pharmaceutical compositions destined for human administration"; correct?
A. That's what's described, yes.
Q. Okay. In addition to teaching about the 1-1 impurity, the specification teaches methods for synthesizing

09:36:21 cabozantinib (L)-malate; correct?
09:36:23 A. Yes.
09:36:24 Q. Okay. The specification includes examples of specific tablet and capsule formulations of cabozantinib (L)-malate; correct?
09:36:34 A. It describes pharmaceutical compositions of cabozantinib (L)-malate.
09:36:40 Q. Okay.
09:36:41 MS. PIROZZOLO: Could -- why don't we go to Joint Exhibit 4, the '349 patent, starting at Column 5, please.
09:36:48 BY MS. PIROZZOLO:
09:36:53 Q. Okay. The patent discloses examples of specific tablet and capsule formulations; correct?
09:37:00 A. Did you say Column 5?
09:37:02 Q. Yes.
09:37:03 A. Yes, there are several compositions described in Column 5.
09:37:11 Q. Okay.
09:37:11 MS. PIROZZOLO: Now, if we go to the claim of the patent on the last page of Joint Exhibit 4.
09:37:17 BY MS. PIROZZOLO:
09:37:20 Q. Claim 3 is directed to a pharmaceutical composition for oral administration; correct?
09:37:26 A. Yes.

Q. And it's a pharmaceutical composition of Compound IB, which is cabozantinib (L)-malate; correct?
A. Yes.
Q. Claim 3 requires that the composition be in a tablet or capsule; correct?
A. Yes.
Q. And Claim 3 also requires that the tablet or capsules be essentially free of the 1-1 impurity; correct?
A. Yes.
Q. Okay. And that means the tablets and capsules must be below 200 PPM of the 1-1 impurity; correct?
A. Yes.
Q. Now, you agree that it's the pharmaceutical composition that must be essentially free of the 1-1 impurity and not the API, per the claim; correct?
A. Yes.
Q. Okay. Now, you've offered the opinion that Claim 3 of the '349 patent is obvious -- is invalid as obvious in view of the prior art; is that right?
A. Yes.
Q. And you're relying on Dr. Lepore to support that opinion; correct?
A. I'm relying on Dr. Lepore's report's opinion about the availability of a cabozantinib (L)-malate salt essentially free of the 1-1 impurity.

Q. So one of Dr. Lepore's opinions you rely on is that the Brown reference discloses a process for making cabozantinib that inherently results in a compound that is essentially free of the 1-1 impurity; correct?
A. Yes.
Q. Now, you're not an expert who performs synthetic chemistry; correct?
A. I do not typically perform chemical synthesis, no.
Q. And you are not offering your own opinion on whether the chemical synthesis process in Brown inherently creates cabozantinib (L)-malate that's free of the 1-1 impurity; correct?
A. That's correct.
Q. Now, you're also relying on Dr. Lepore's alternative opinion that a skilled artisan would have a reasonable expectation of success in adding a recrystallization step to make cabozantinib (L)-malate essentially free of the 1-1 impurity; correct?
A. Yes.
Q. You rely on his opinion because you haven't thought about any recrystallization schemes that could be used; correct?
A. I have -- I thought about recrystallization in concept as a purification methodology, and I'm well aware of that methodology. I haven't thought about specific

09:39:50 recrystallization purification schemes for cabozantinib (L)-malate.
09:39:53 Q. Okay. So, you haven't thought about any recrystallization schemes that could be used to create cabozantinib (L)-malate that's free of the 1-1 impurity; correct?
09:40:04 A. No. No, I have not.
09:40:06 Q. Now, you're not claiming that Brown -- the Brown reference inherently discloses a pharmaceutical composition of Claim 3; correct?
09:40:15 A. Not inherently. I am -- it doesn't -- it describes pharmaceutical compositions. It describes all of the components of the Claim 3 composition.
09:40:28 Q. Okay. But my question was: You're not claiming Brown inherently discloses a pharmaceutical composition of Claim 3; correct?
09:40:36 A. And it would help if you would explain to me what you -- why you're emphasizing inherently.
09:40:46 Q. Because I'm talking --
09:40:47 A. Or show me. Have I provided an opinion where I have stated that Brown inherently describes the pharmaceutical composition?
09:40:55 Q. Well, let's go to your deposition.
09:40:58 MS. PIROZZOLO: It's Tab 4, Volume I, if we pull it up. Okay. At Page 160, Lines 21, to 161, Line 2.

09:41:20 And you were asked:

09:41:22 "QUESTION: You're not offering an opinion that the composition with claimed characteristics was inherent in the prior art?"

09:41:29 And you said, "I think the API composition and its being free from the quinol impurity is inherent from the prior art. The rest of the formulation aspects of the prior art are obvious."

09:41:41 BY MS. PIROZZOLO:

09:41:44 Q. Is that your opinion?

09:41:45 A. Yes, that's my opinion.

09:41:48 Q. Now, you've worked at the University of Iowa College of Pharmacy since 1989; correct?

09:41:53 A. Yes.

09:41:54 Q. And you've worked on formulation issues -- issues for about four decades?

09:41:59 A. That's fair, yes.

09:42:01 Q. Okay. You have not developed a formulation of a commercially marketed drug; correct?

09:42:05 A. No, that hasn't been my focus.

09:42:08 Q. Okay. Now, you have testified it would be obvious to make a pharmaceutical composition of cabozantinib (L)-malate essentially free of the 1-1 impurity; is that right?

09:42:18 A. Yes.

09:42:19 Q. Okay. The API is the active pharmaceutical

09:42:23 ingredient; correct?
09:42:24 A. Yes.
09:42:25 Q. A drug product is the pharmaceutical product that includes the API and potentially other excipients; correct?
09:42:32 A. Yes.
09:42:34 Q. Now, each API has unique properties; correct?
09:42:37 A. Typically, yes.
09:42:40 Q. These unique properties include how the API reacts with other chemicals; correct?
09:42:45 A. Yes.
09:42:46 Q. And every API does not react the same way to temperature; correct?
09:42:54 A. Not exactly the same way, no.
09:42:56 Q. APIs can also interact with water in different ways; correct?
09:43:00 A. Potentially, yes.
09:43:01 Q. Okay. Now, the presence of impurities in an API would often suggest that those same impurities would be present in the final pharmaceutical composition; correct?
09:43:13 A. It would be suggestive of that, yes.
09:43:15 Q. Okay. And that would occur unless there was some attempt to remove them; correct?
09:43:21 A. Usually.
09:43:22 Q. Okay. Now, degradation products are a type of impurity; correct?

09:43:27 A. Yes.
09:43:28 Q. Degradation products may occur during formulation; correct?
09:43:32 A. They can and this is why we do excipient compatibility studies.
09:43:36 Q. Degradation impurities can occur during the production of steps used to reach a final dosage form; correct?
09:43:43 A. They can and we oftentimes check for those even in preformulation and formulation activities.
09:43:48 Q. Okay. Hydrolysis is a degradation reaction that can occur in drug products; correct?
09:43:55 A. Yes, it can.
09:43:56 Q. Excipients can interact with an API in a way that causes degradation; correct?
09:44:01 A. Yes. And, again, that's why we do excipient compatibility studies.
09:44:04 Q. Okay. And excipients -- for example, degradation could occur through oxidation; correct?
09:44:10 A. That is a known degradation pathway, yes.
09:44:14 Q. And you can't predict in advance every reaction that might occur between an excipient and the API; correct?
09:44:20 A. You can't predict every -- every one of them. Oftentimes we have indicators of suspicion based on the materials and their chemical properties and previous

behaviors. And, again, that's why we do excipient compatibility studies.

Q. So, you perform experiments to determine whether the excipient is compatible with the FDA -- with the API; correct?

A. Yes. And we choose -- choose -- oftentimes try to choose excipients initially that we think will be compatible, but we do the experiments to confirm. And those are routine, they're done all the time.

Q. Wet granulation is a technique used in pharmaceutical formulation; correct?

A. In -- yes. For tablet production, frequently.

Q. And wet granulation can expose an API to heat; correct?

A. It can, yes.

Q. And exposing an API to heat and humidity during a pharmaceutical manufacturing process can cause degradation; correct?

A. It can. We can limit those oftentimes.

Q. Well, I'm just asking whether it can.

A. It can.

Q. Degradation impurities can also form during drug storage; correct?

A. Yes, they can.

Q. And drug formulation involves experimentation,

observation, and optimization; correct?
A. Yes.
Q. In order to address degradation, a skilled artisan seeks to understand the degradation pathway; correct?
A. Can you repeat that?
Q. In order to address degradation, a skilled artisan seeks to understand the degradation pathway; correct?
A. They might not try to fully characterize the entire reaction mechanism, but they may want to be at least knowledgeable about which functional groups and which molecules seem to be participating in a degradation reaction.
Q. So, they might want to be knowledgeable about how the degradation is occurring?
A. To a limited extent, potentially.
Q. Now, I want to turn to what the prior art disclosed about the 1-1 impurity in pharmaceutical compositions. Okay?
A. Okay.
Q. You've discussed several prior art references during your direct examination today; correct?
A. Yes.
Q. None of the prior art references you discussed describe the mechanisms of degradation of cabozantinib (L)-malate; correct?

09:46:52 A. That's correct.
09:46:54 Q. Nothing in the prior art taught that temperature was a factor in the formation of the 1-1 impurity in cabozantinib (L)-malate; correct?
09:47:02 A. Not specifically, no.
09:47:04 Q. Nothing in the prior art has information about the role of water in the formation of the 1-1 impurity; correct?
09:47:10 A. Not specifically about cabozantinib.
09:47:13 Q. Nothing in the prior art spoke to the formation of 1-1 impurity under formulation relevant conditions; correct?
09:47:20 A. Nothing specifically about cabozantinib.
09:47:24 Q. Nothing in the prior art indicated whether the formation of the 1-1 impurity in cabozantinib (L)-malate was pH-dependent; correct?
09:47:32 A. No, nothing specifically about cabozantinib.
09:47:34 Q. Okay. You have not cited any reference that explains how to reduce the formation of the 1-1 impurity in a drug product; correct?
09:47:42 A. Not specifically -- wait. I'm sorry. Can you say that again?
09:47:45 Q. You have not cited any reference that explains how to reduce the formation of the 1-1 impurity in a drug product?
09:47:53 A. Not specifically about the 1-1, yes.
09:47:56 Q. You are not aware of any actual formulation of cabozantinib (L)-malate disclosed in the prior art; correct?

09:48:03 A. No, I am not.
09:48:05 Q. You haven't identified any prior art reference that discloses the physicochemical properties of cabozantinib (L)-malate; correct?
09:48:13 A. That's correct.
09:48:15 Q. Now, I'd like to look more closely at some of the references you discussed.
09:48:20 MS. PIROZZOLO: If we could pull up the Brown reference, which is Defendants' Exhibit 291, which is at Tab 7 in your binder.
09:48:27 BY MS. PIROZZOLO:
09:48:40 Q. Now, the Brown reference does not say that the 1-1 impurity is genotoxic; correct?
09:48:45 A. That's correct.
09:48:49 MS. PIROZZOLO: Let's turn to paragraph 82 in Brown, which you discussed earlier.
09:48:53 BY MS. PIROZZOLO:
09:48:58 Q. Brown doesn't disclose any specific pharmaceutical compositions of cabozantinib (L)-malate; correct?
09:49:04 A. They provide -- they provide general descriptions of pharmaceutical compositions.
09:49:12 Q. There are no specific examples of pharmaceutical compositions; correct?
09:49:16 A. No, there are not.
09:49:18 Q. Now, Brown does not mention the word "glidant." Does

09:49:22 it?
09:49:23 A. Not specifically as the word.
09:49:27 Q. Now, you testified about some guidelines for control
09:49:32 of impurities.
09:49:33 Do you recall that?
09:49:34 A. Yes.
09:49:34 Q. The regulatory guidances you mentioned?
09:49:36 A. Yes.
09:49:37 Q. Okay. The references you discussed are general
09:49:40 guidances for developers; correct?
09:49:42 A. Yes.
09:49:44 Q. Okay. You have not identified any FDA guidance
09:49:47 documents for controlling impurities in cabozantinib
09:49:51 (L)-malate; correct?
09:49:51 A. Not specific to cabozantinib (L)-malate.
09:49:54 Q. Now, you also testified about Lachman, the volume on
09:50:00 pharmaceutical dosage forms.
09:50:01 Do you recall that?
09:50:01 A. Yes.
09:50:03 Q. Okay. And that's a general reference on formulation;
09:50:07 correct?
09:50:07 A. Well, it's a well-known textbook series. Yes.
09:50:10 MS. PIROZZOLO: Okay. Let's turn -- Lachman is
09:50:13 Tab 8 in your binder. And we have an excerpt that's
09:50:18 Plaintiff's Exhibit 553A.

Could you turn to Page 76 at Tab 8?

There's a paragraph at the top of the page, but I'd like to highlight the sentence beginning with --

THE WITNESS: Can you wait just a moment? I was looking at the PDF pages.

BY MS. PIROZZOLO:

Q. Sure.

A. Okay. Thank you.

Q. Okay. Lachman says, "The correct selection and balance of excipient materials for each active ingredient or ingredient combination in a tablet formulation to achieve the desired response (i.e. production of a safe, effective, and highly reliable product) is not in practice a simple goal to achieve."

Is that what Lachman says?

A. It does say that. Yes.

Q. Now, you talked about a section on exemplary formulations in Lachman; correct?

A. Yes.

Q. Lachman doesn't have a description of how to control for genotoxic impurities in those formulations; correct?

A. No, but there are sections that -- that describe that a formulator needs to be aware to control for impurities in a formulation.

Q. Okay. But those specific formulations, there's no

description of how to control for genotoxic impurities using them; correct?

A. Not associated directly on the page with those examples.

Q. Okay. Now, you testified about the '081 application, which is Defendants' Exhibit 335. And it's Tab 9 of your binder.

The '081 patent application discloses the tyrosine kinase inhibitors, such as gefitinib, erlotinib and lapatinib can be formulated as tablets or capsules; correct?

A. I believe those were the specific examples of tyrosine kinase inhibitors that were the focus of the '081.

Q. You haven't compared the chemical structure of those tyrosine kinase inhibitors to cabozantinib (L)-malate; correct?

A. Not in any serious manner.

Q. Okay. And you don't know whether those tyrosine kinase inhibitors have similar physicochemical properties to cabozantinib; correct?

A. That's correct.

Q. You have not identified a specific pharmaceutical composition of cabozantinib (L)-malate that would be obvious over the prior art and inherently and essentially free of the 1-1 impurity; correct?

A. That was in the prior art?

Q. Yes.

A. Not -- not a cabozantinib specific containing formulation in the prior art. But there were formulations that would likely be successful as far as pharmaceutical compositions -- compositions that cabozantinib (L)-malate could be used with.

Q. But you haven't identified a specific pharmaceutical composition of cabozantinib (L)-malate that would be obvious over the prior art and essentially free of the 1-1 impurity; correct?

A. Not one that is described to provide or to contain cabozantinib (L)-malate and other specific excipients at specific amounts.

Q. Now, you've offered the opinion that given cabozantinib (L)-malate that was essentially free of the 1-1 impurity, it would have been obvious -- a skilled artisan would have been motivated and found it obvious to prepare a pharmaceutical composition inherently free of the 1-1 impurity; right?

A. Yes.

Q. You can't recall ever having purified a pharmaceutical product in order to eliminate genotoxic impurities; correct?

A. No. That just hasn't been the focus of my research program.

09:54:43 Q. You've never worked to control genotoxic impurities in a product that was in clinical trials; correct?
09:54:48 A. No, I haven't.
09:54:49 Q. Okay. Now, I'd just like to briefly touch on your opinion on secondary considerations.
09:55:01 A. Okay.
09:55:03 Q. You don't dispute that Exelixis' product, Cabometyx, embodies Claim 3 of the '349 patent; correct?
09:55:11 A. No, I don't.
09:55:13 MS. PIROZZOLO: I have no further questions.
09:55:15 THE COURT: All right. Redirect?
09:55:17 MR. MATHAS: No, Your Honor. No questions. I do have some exhibits to move.
09:55:20 THE COURT: All right. So, Dr. Donovan, you're done. You can step down. Watch your step.
09:55:24 Yes, Mr. Mathas.
09:55:25 MR. MATHAS: All right. We move the admission of DTX-284, DTX-335, DTX-325, DTX-192, DTX-013, and PTX -- strike that last one, Your Honor. I need to check that. So I'm going to stop at DTX-013 for now.
09:55:59 MS. PIROZZOLO: Oh, no objection.
09:56:00 THE COURT: All right. Admitted without objection.
09:56:02 (DTX Exhibit No. 13, 192, 284, 325 and 335 were admitted into evidence.)

MR. MATHAS: And that's all, Your Honor. Thank you.

MR. COOPER: Your Honor, MSN calls Dr. Jonathan Steed.

THE COURT: All right.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: Yes. Jonathan William Steed. J-O-N-A-T-H-A-N, W-I-L-L-I-A-M, S-T-E-E-D.

JONATHAN WILLIAM STEED, the witness herein, after having been duly affirmed under oath, was examined and testified as follows:

MR. COOPER: May I proceed?

THE COURT: Sure.

MR. COOPER: Thank you, Your Honor.

Oh, there's two volumes. Okay.

THE COURT: So, Dr. Steed, do you know how many times you've testified before me before?

THE WITNESS: This must be at least the third time, Your Honor.

THE COURT: Okay.

THE WITNESS: Hello again.

THE COURT: Go ahead, Mr. Cooper.

DIRECT EXAMINATION

BY MR. COOPER:

09:58:32 Q. Good morning. Could you please reintroduce yourself to the Court?
09:58:35 A. Yes. My name is Jonathan Steed. I'm professor of chemistry at Durham University in the U.K.
09:58:41 Q. Dr. Steed, have you prepared slides to assist in explaining your testimony today?
09:58:44 A. I have. Yes.
09:58:45 Q. Okay.
09:58:46 MR. COOPER: For the record those slides are on the screen and marked in the bottom right-hand corner as DDX-Steed and then the slide number.
09:58:49 BY MR. COOPER:
09:58:54 Q. I'd first like to ask you briefly about your education, employment and qualifications.
09:58:58 MR. COOPER: Mr. Figera, could we please pull up DTX-558?
09:59:00 BY MR. COOPER:
09:59:03 Q. Dr. Steed, could you tell us what this document is?
09:59:05 A. Yes, that's my CV.
09:59:07 Q. Does it accurately describe your employment, education and publications?
09:59:10 A. It does.
09:59:12 MR. COOPER: Let's go to DDX Steed 2.
09:59:12 BY MR. COOPER:
09:59:15 Q. What are your primary areas of teaching and research?

09:59:18 A. I research crystallization methods, pharmaceutical solid forms and also synthetic chemistry.
09:59:26 Q. And how long have you worked in the field of chemistry and crystalline forms?
09:59:31 A. Over 30 years now.
09:59:32 Q. Have you published any peer-reviewed papers or books relating to crystalline pharmaceutical salts and characterization methods?
09:59:40 A. Yes, I have over 350 papers, along with a number of books that I both edited and written.
09:59:45 Q. Are you involved in any scientific journals?
09:59:48 A. Yes, I'm editor in chief of the *American Chemical Society Journal Crystal Growth & Design* which specializes in this area.
09:59:54 Q. Are you a member of any associations in the field?
09:59:56 A. Yes, I'm a fellow of the Royal Society of Chemistry. I'm a member of the American Chemical Society and the British Crystallographic Association.
10:00:04 Q. Have you briefly been accepted as an expert in United States district courts in Delaware and elsewhere?
10:00:09 A. I have.
10:00:11 MR. COOPER: Your Honor, MSN tenders Dr. Jonathan Steed as an expert in the formation, characterization and use of pharmaceutical salts.
10:00:19 MR. PRUSSIA: No objection.

THE COURT: All right. You may proceed.

BY MR. COOPER:

Q. Dr. Steed, have you been engaged by MSN to render an opinion on whether the '439, the '440 and '015 patents in suit in this case are valid or not?

A. I have. Yes.

Q. And for brevity can we refer to those patents collectively as the malate salt patents or crystalline malate salt patents today?

A. We can.

MR. COOPER: Mr. Figera, can we please pull up JTX-1?

BY MR. COOPER:

Q. Dr. Steed, what do you recognize JTX-1 to be?

A. So this is the '439 patent.

Q. When did the '439 patent issue?

A. August 17th, 2021.

MR. COOPER: Can we please pull up JTX-2?

BY MR. COOPER:

Q. Dr. Steed, what do you recognize JTX-2 to be?

A. That's the '440 patent, August 17th, 2021, as well.

MR. COOPER: Can we please pull up JTX-3?

BY MR. COOPER:

Q. Dr. Steed, what do you recognize JTX-3 to be?

A. That's the '015 patent, August 24th, 2021.

Q. Do you understand that the three malate salt patents share the same specification?
A. Yes.
Q. Have you reviewed the asserted claims of these patents?
A. I have. Yes.
MR. COOPER: Let's go to DDX Steed 3.
BY MR. COOPER:
Q. Dr. Steed, could you explain what the asserted Claim 4 of the '439 patent requires?
A. Yes. Claim 4 depends upon Claim 3, which in turn depends upon Claim 1. And it requires cabozantinib malate salt, specifically the (L)-malate salt where the salt is crystalline.
Q. Dr. Steed, what does the asserted claim of the '440 patent require?
A. It requires that same crystalline cabozantinib (L)-malate salt as part of the pharmaceutical composition.
Q. What does the asserted Claim 2 of '015 patent require?
A. Crystalline cabozantinib malate salt, using a method for treating cancer, specifically kidney cancer.
MR. COOPER: Let's go to Page 2 of JTX-1 and call out the application number and the date of the U.S. application data.

BY MR. COOPER:
Q. Dr. Steed, when was the application filed from which the '439 patent issued?
A. October 14th, 2020.
Q. Were the applications from which the '440 patent and '015 patent issued filed after that?
A. Yes.
Q. What do you understand Exelixis claims to be the priority date for all of the malate salt patents?
A. It's January the 16th, 2009.
Q. If I use the term "prior art" today, will you understand that to mean published materials available to a POSA, or a person of ordinary skill in the art, before January 16th, 2009?
A. I will, yes.
MR. COOPER: Let's go to DDX Steed Slide 4.
BY MR. COOPER:
Q. Dr. Steed, before we get into the details today, can you please provide the Court with a brief overview of the testimony you're going to give today on whether the malate salt patents lack written description.
A. Yes. It's my opinion that they do lack written description. A person of skill would understand the inventors were not in possession of all crystalline cabozantinib malate salts. In other words, they weren't in

possession of the full scope of the claims.

And, moreover, the two species that Exelixis does -- does discuss within the patents' specification are not themselves representative of the full scope of the claims, in other words, all the possible crystalline cabozantinib (L)-malate salts.

Q. Can you also provide a brief overview of what you'll be discussing on whether the malate salt patents are invalid for obviousness-type double patenting?

A. Yes. It's my opinion they are invalid for obviousness-type double patenting over Claim 5 of the earlier '473 patent that we've already heard about today. I don't feel there's any meaningfully patentably distinct differences between that Claim 5 and the malate salt patents.

So the '473 patent is -- distinguishes pharmaceutically acceptable cabozantinib salts in the genus, and that includes the species, crystalline cabozantinib (L)-malate salt species. And the published priority application, the '928 application, discloses compositions and the treatment of kidney cancer.

MR. COOPER: Let's go to DDX Steed Slide 5.

BY MR. COOPER:

Q. When you were forming your opinions in this case, did you consider the issues from the perspective of a POSA?

A. I did. Yes.

Q. And can you read the definition of a POSA that you applied to your analysis?

A. Yes. So a POSA would have a doctorate or a lesser graduate degree in chemistry, pharmaceutical sciences or related discipline. I think they would have three years or greater experience working with analytical techniques used to characterize forms of drug substances. And they would have collaborated with others so the team would collectively have had experience in synthesizing and analyzing complex small molecule compounds or a physician with experience in administration, dosing and efficacy of drugs for the treatment of a particular disease state.

Q. Would your opinions in this case change if the definition of a POSA proposed by Exelixis on the right-hand side of the slide is adopted?

A. No, they wouldn't.

Q. Were you yourself a POSA as of the priority date using either party's proposed definition?

A. I was.

MR. COOPER: Can we move to DDX Steed 6?

BY MR. COOPER:

Q. And let's start with the discussion of the technical background and state of the prior art before getting into the details of your invalidity opinions.

MR. COOPER: Let's move to DDX Steed 7.

BY MR. COOPER:

Q. Now, first, the asserted claims refer to a salt, cabozantinib (L)-malate.

Dr. Steed, can you explain what a salt is?

A. Yes. As we've already heard, a salt is the product of a reaction of an acid with a base.

Q. And what are you showing on DDX-7?

A. Here on this slide, I'm showing simply the formation of very common table salt, sodium chloride. So the acid in question is hydrochloric acid, HCl, that reacts with sodium hydroxide, a base. And the hydrogen ion and the sodium ions swap over to give a sodium chloride, common salt. And the byproduct is water.

Q. Are pharmaceutical compounds ever made into salts for use as active pharmaceutical ingredients?

A. Yes, very commonly, around half the time or so. Pharmaceutical salts can have considerable advantages in terms of delivering an active ingredient to the body.

Q. Did the prior art report on any benefits of developing salts for use as active ingredients in pharmaceutical products?

A. Yes, it did.

MR. COOPER: Can we pull up DTX-177? And call out the title?

By MR. COOPER:

Q. Dr. Steed, what is this exhibit?

A. So, this is a prior art document entitled "Trends in Active Pharmaceutical Ingredient Salt Selection Based on Analysis of the Orange Book Database."

And it's by first author Paulekuhn.

MR. COOPER: Can we call out the introduction on Page 1 of this exhibit?

BY MR. COOPER:

Q. Dr. What does Paulekuhn report --

(Reporter clarification.)

BY MR. COOPER:

Q. I'm sorry.

Doctor, what does Paulekuhn report about the use of salt formation in pharmaceutics?

A. Yes, Paulekuhn confirms that salt formation is a well-known technique to modify and optimize the physical chemical properties of a drug substance. And Paulekuhn calls out some examples of those sorts of properties; solubility, dissolution rate, the speed at which the -- the drug substance dissolves in the body, hygroscopicity, its propensity to absorb moisture, stability, impurity profiles, and crystal habit, the shape which affects properties and characteristics.

Q. At the priority date, what percentage of drug

products approved by the FDA had API in salt form?
A. Around half.
Q. Were there methods described in the prior art about how to prepare pharmaceutical salts and test their properties?
A. Yes, there were.
MR. COOPER: Let's go to DDX Steed Slide 8.
BY MR. COOPER:
Q. Are there typical steps that a POSA goes through in testing or preparing salts?
A. Yes. I'm showing the four steps of what's called a salt screening process in which a person of skill carries out an experimental procedure in which they -- they identify and optimize the salt forms of the pharmaceutical.
Q. In pharmaceutical development, what entity typically performs salt screening activities?
A. It's a routine activity, so it's often outsourced to a contract research organization.
Q. How long does a salt screen typically take?
A. It can be really quite quick. Each of the individual experiments are really quite brief. And so, a salt screen can be completed in a matter of a few weeks.
Q. Can you describe the typical first step of a salt screen?
A. Yes. That usually involves solubility tests of the

10:08:38 active pharmaceutical ingredient. And so, a person of skill
10:08:41 or the contract research organization will test the
10:08:44 solubility of the -- in this case, free base, the non-salt
10:08:48 form, within a variety of common laboratory solvents.
10:08:52 Q. How does a POSA choose the -- what to perform these
10:08:57 solubility tests in?
10:08:58 A. They would use solvents that are known in the art and
10:09:01 common in the laboratory. There may be some tens of
10:09:05 solvents. Each individual experiment is very brief and so
10:09:08 many solvents can be screened.
10:09:09 Q. And when you say "very brief," what do you mean?
10:09:11 A. Literally a matter of a few minutes to -- to add
10:09:16 solvent to -- to the active pharmaceutical ingredient. And
10:09:19 observe the amount that dissolves.
10:09:21 Q. Can describe the typical second step of a salt
10:09:24 screen?
10:09:24 A. Yes, then once solutions of the pharmaceutical
10:09:29 ingredient are available, then acids or bases have to be
10:09:31 selected. Those will provide the non-pharmaceutically
10:09:34 active counter ion in the salt. On the basis of a --
10:09:39 various roles and compatibility with -- with the active
10:09:43 ingredient.
10:09:44 Q. How many potential counterions are typically tested
10:09:46 in one salt screen?
10:09:47 A. Something of the order of 15 to 20.

Q. Does the prior art identify counterions that were known to be pharmaceutically acceptable?
A. Yes. It does.
MR. COOPER: Let's go to DDX Steed Slide 9.
BY MR. COOPER:
Q. What are you showing on this slide?
A. So these are abstracts from three prior art documents that have lists of counterions that have been used in pharmaceutical drug products in the past.
Q. And what are the prior art references that you've reviewed that contain these lists you're referring to?
A. Yes, so these lists are quite common. So one is taken from that Paulekuhn reference that I was identifying earlier, that's DTX-177 at Page 3. There's also a reference by a first author Bighley, DTX-167 at Page 4. And first author, Berge, DTX-166 at Page 2.
Q. And approximately how many FDA-approved pharmaceutically acceptable acid counterions are consistently identified in these prior art lists?
A. There's maybe around 50 or so.
Q. And malate is the acid counter -- malic acid is the acid counterion at issue in this case. Does it appear on these prior art lists you've identified?
A. Yes, it appears on all of them.
Q. Does the prior art provide any guidance to a POSA

about selecting acid or base counterions that will predictably form salts in a salt screen?

A. It does, yes.

MR. COOPER: Can we please pull up DTX-243 and call out the title?

BY MR. COOPER:

Q. Dr. Steed, what is this exhibit?

A. This is a prior art document entitled "In Situ Salt Screening - a Useful Technique For Discovery Support and Preformulation Studies," first author Tong.

MR. COOPER: Let's go to Page 4 of this exhibit and call out the first part of the method section, down through Step 1.

BY MR. COOPER:

Q. And at step one there's a reference to pK_a. Could you explain what that refers to?

A. Yes, pK_a is a measure of the acidity of an acid in this case, or basicity of a base, it's how acidic something is and how -- how strong it's propensity is to form a salt.

Q. Is pK_a an inherent property of a compound?

A. It is, yes.

Q. How --

A. That's the molecular structure.

Q. How is the pK_a of a compound of interest and its counterion measured?

A. It's a straightforward experimental technique called titration that can be done in an automated way.

Q. What instruction does Tong provide to a POSA about acid selection?

A. Tong teaches that in order to form a salt, the acid needs to be strong enough to transfer a hydrogen ion to a base. And so the acid should be at least two pH units lower than the pK_a of the compound and the base in question in this case.

Q. What would a POSA expect if the pK_a difference between an acid and a base is greater than two?

A. They would expect a solid salt to result.

Q. And why is that?

A. Because the acid is strong enough to transfer a hydrogen ion to the base.

MR. COOPER: Let's go to DDX Steed Slide 10.

BY MR. COOPER:

Q. Could you explain what is the third typical step of a salt screen?

A. Yes. Well, then having identified, in this case, acids that can form salts with bases in solution, the person of skill would then crystalize the range of their acid base choices under a range of different experimental conditions, looking to sample the possible crystallization space to maximize their ability to isolate solids, hopefully

crystalline solids.

Q. What are the types of experimental conditions that a POSA would typically vary in order to crystalize a salt out of solution?

A. So, those might be things like crystallization method, slow evaporation, cooling temperature, solvent, those sorts of things.

Q. Will a POSA be able to crystallize out of solution all of the pharmaceutical salts that are formed during a salt screen?

A. Not all of them, no. But typically they would be able to isolate a solid, most of them, if only by evaporating off the solvent and then characterize what the result was.

Q. What is the typical last step of a salt screen?

DEPUTY CLERK: Could you slow down just a little bit.

THE WITNESS: Sorry.

BY MR. COOPER:

Q. Could you explain what the typical last step of a salt screen is?

A. Yes. In whatever solids arise from that crystallization attempts, then the person of skill would use routine analytical techniques to characterize the outcome, characterize the residual solids.

Q. And what are the typical properties that will be characterized for each salt that's prepared in a screen?

A. So typically it's crystallinity using x-ray powder diffraction. The sort of properties I alluded to earlier; hygroscopicity, melting point, it's -- whether it's a solvate or not, those sorts of things.

MR. COOPER: Let's go to DDX Steed Slide 11.

BY MR. COOPER:

Q. And you mentioned one of the properties of a salt is its crystallinity. Can you explain the different -- what that is?

A. Yes. So the outcome of the salt screen, if it's a solid it might be either amorphous or crystalline. If it's a crystalline solid, then there will be a regular repeating array of the molecules that give rise to the crystal structure.

Q. Could you describe what you've shown on the left-hand side of this slide titled "Crystalline Salts" to help you explain that further?

A. Yes. So here's a diagram of a randomly chosen drug, it's a heart drug called xylazine hydrochloride. That exists in at least two crystalline forms. They happen to be called forms 1 and form 3. And you can see from the diagrams there, that they have a different packing arrangement of the xylazine molecules in each of the two

different forms that I'm showing there.

So both of them are crystalline, both of them have a theoretically infinite repeating array of the molecules. But the arrangement of the molecules is different. So if -- and that's characterized by the box that I'm showing there, which is the -- the unit cell.

So if the crystal is a brick wall, the unit cell will be the bricks that it's made up of. And different crystalline salts have different -- made up of different bricks, different packing arrangements.

Q. Now, we heard during Exelixis' opening statements that the asserted claims don't have the word "form" in them.

Do you recall that?

A. I do. Yes.

Q. Doctor, what would a POSA understand about a salt that is crystalline?

A. In order to be crystalline, a salt has to have a regular repeating underlying arrangement. That's what crystallinity is. And so it will be in a particular crystalline arrangement, which we give the term crystal form to. You can't be crystalline without having an underlying arrangement without being in a crystal form.

Q. How is it possible to prepare a different crystalline forms of the same salt compound?

A. The crystalline form that comes out -- we sometimes

10:16:30 use the words polymorph for different crystalline forms that have the same composition -- arises from the different circumstances under which it's formed. So different crystallization methods will give rise to different crystalline arrangements.

Q. Can you describe now what you've shown on the right-hand side of this slide titled "Amorphous salt"?

A. Yes. So if something is amorphous, then it doesn't have crystallinity. It doesn't have an underlying repeating regular arrangement and the molecules are randomly arranged and so there is no unit cell, there's no brick making up the brick wall. It's just like a pile of rubble.

Q. Can both crystalline and amorphous salts be pharmaceutically acceptable for use in drug products?

A. Yes, they can. Typically crystalline is preferred because crystalline salts are usually more stable, often less hygroscopic and so on, but amorphous -- amorphous drug substances are known and are used.

Q. You mentioned crystalline is preferred. Does the prior art report any statistics about the amount of that preference in the use of pharmaceuticals?

A. Yes. It's a strong preference. Over 90 percent of drugs are administered in crystalline form.

MR. COOPER: Can we please pull up DTX-392?

BY MR. COOPER:

Q. Dr. Steed, what is this exhibit?
A. So this is a prior art, a book reference entitled *Pharmaceutical Preformulation and Formulation*, edited by Gibson.
MR. COOPER: Let's go to Page 27 of the exhibit. And call out the part of that page that is under "amorphous forms." And look at paragraphs 2 and 3.
BY MR. COOPER:
Q. What is this reference report about amorphous forms?
A. Yeah. Gibson teaches a preference for crystalline. So he says: Because of these problems with physical and chemical stability that I was alluding to, it's not usual to proceed into development with a candidate drug in such a state, in other words in the amorphous state. Attempts to crystalize the amorphous phase should always be undertaken.
Q. So what motivation, if any, does a POSA have to prepare a crystalline salt of a drug compound?
A. A strong motivation. Typically, you wouldn't want to use an amorphous salt unless there was a particular reason to do so, such as a need for the high -- usually the high solubility of amorphous.
MR. COOPER: Let's pull up DTX-191.
BY MR. COOPER:
Q. Dr. Steed, what is this exhibit?
A. This is a prior art reference entitled, "Crystalline

solids," first author Vippagunta.

MR. COOPER: Let's go to Page 2 of this exhibit and call out the bottom left-hand paragraph.

BY MR. COOPER:

Q. Doctor, what does Vippagunta report about crystalline forms here?

A. Yes. So, Vippagunta is really confirming my definition of crystalline polymorphs as different crystalline forms of the same chemical substance, and he says that they have the same chemical composition but differ in terms of crystal structures and, therefore, they possess different physiochemical properties, the properties come from their underlying structure. And he gives -- and he goes on to say that's occurrence of polymorphism is quite common among organic molecules such as drugs.

Q. How does a POSA identify the internal crystalline structure of a compound?

A. They would use compound physical techniques, which by far the most common would be X-ray powder diffraction.

MR. COOPER: Let's go to DDX Steed Slide 12.

BY MR. COOPER:

Q. Can you first, briefly, explain how XRPD works?

A. Yes. So, a sample of the -- of the powder, which is really a bunch of randomly arranged crystals -- more crystals is placed on the sample stage. It's radiated with

X-rays and the X-rays are scattered by the underlying regular repeating array of molecules. And that scattering results in the kinds of patterns that we're seeing here. So a plot of scattered X-ray intensity, as a function of the angle that's scattered through, which we call two-theta.
Q. This slide calls out Figure 13B and E from Page 18 of the Vippagunta reference. Can you explain what's shown in this figure?
A. Yes. Just as an example of X-ray powder diffraction, they've begun to show some powder diffraction patterns of two polymorphs, two different crystalline forms of the artificial sweetener aspartame. And you can see that in B and E they have a different pattern of peaks spread across the two-theta range 5 to 30 degrees.
And by looking at the whole pattern as a whole, you can see that these two patterns are different and so therefore these are two different crystalline forms of aspartame.
Q. In addition to the structural differences you've described, do different crystalline forms of salt -- of a salt compound have different physical or chemical properties?
A. Yes, they do. Each crystalline polymorph or, for that matter, solvated crystalline form will have its own set of unique physical and chemical properties that stem from

the underlying different structure.

MR. COOPER: Let's go to DDX Steed Slide 13.

BY MR. COOPER:

Q. And what have you listed on this slide?

A. Yes. So this is a list of all the intrinsic properties of crystalline salt forms, or at least a representative array. It's probably not all of them. So, obviously, the crystal structure. And then properties, such as melting point, hygroscopicity, the propensity to absorb moisture, the physical and chemical stability. So, whether the form will remain the same crystalline form and whether it will remain the same molecules depends upon the solid form. The solubility, and the rate that at which it will dissolve both depend upon the solid form that it starts in, the bioavailability and the process and characteristics. All of those are intrinsic properties that depend upon the particular crystalline form.

Q. Could you describe specifically what melting point refers to?

A. Yes. Melting point is the temperature at which a solid transforms to a liquid. And in pharmaceutical development, typically you would want a reasonably high melting point so you don't get sticky or -- sticky materials.

Q. What does hygroscopicity of a crystalline salt refer

to?
A. That's the propensity of a solid to absorb moisture. And typically a low hygroscopicity is preferred so that you don't get weight changes upon pharmaceutical formulation.
Q. What does physical and chemical stability of a crystalline salt refer to?
A. The physical stability is whether the solid form remains stable over time. So whether the -- to ensure that there's not a change from one polymorph to another or desolvation of a solvate or something like that. The chemical stability is whether the molecules themselves degrade over time. So you don't want a good drug molecule turning to into a bad degradation impurity, for example.
Q. What does solubility of a crystalline salt refer to?
A. It's how much will dissolve in a solution under a given set of conditions.
Q. What does dissolution rate of a crystalline salt refer to?
A. Somewhat related to solubility. It's how fast it will dissolve into a given solvent under a given set of conditions.
Q. What does processing characteristics refer to?
A. That's things like how we can just filter the material, which might depend upon the crystal shape. How it gets compressed into a tablet. Those sort of mechanical

aspects.
Q. What does bioavailability of a crystalline salt refer to?
A. That's the percentage of the dosage form -- the active ingredient in the dosage form that actually makes it into the bloodstream so they can have -- so that it can exert its therapeutic effect. It depends, to some extent, on solubility and dissolution rate.
Q. And would a POSA expect one crystalline salt form of a compound to have the same or similar properties as another crystalline form of the compound?
A. No. Each crystalline form will have its own set of properties. Some of them may be similar to each other. Other properties may be very distinct. It depends upon the underlying crystalline structure.
Q. Does FDA provide any relevant guidance resulting from the fact that different crystalline forms have different physical and chemical properties?
A. It does. Yes.
MR. COOPER: Can we pull up DTX-170?
BY MR. COOPER:
Q. Dr. Steed, what is this exhibit?
A. So this is the FDA's guideline for submitting supporting documentation in drug applications for the manufacture of drug substances; and this is the 1987 first

edition, if you like.

MR. COOPER: Let's go to Page 35 of the exhibit. And call out the bottom paragraph.

BY MR. COOPER:

Q. What guidance does FDA provide here?

A. Yeah. The FDA says that by the time of a new drug application submission, the applicant should have established whether -- whether or not the drug substance exists in multiple solid state forms, in other words polymorphs, and whether these affect the dissolution and bioavailability of the drug product.

Q. Why is it important to FDA to determine whether a pharmaceutical salt exists in multiple crystalline forms?

A. Because each will have different pharmaceutical properties of the type that I've just alluded to. And if there's a change on storage or in formulation, that might affect those properties, perhaps undesirably.

Q. Are there any well-known examples where the properties of a crystalline form have affected the function of a drug?

A. There are many examples, perhaps the most famous one is ritonavir in which Abbott Labs had, first of all, just one form of ritonavir which they formulated as an anti-HIV medication in the late 1990s, when it went to market, a second, less soluble, more stable crystalline form appeared

and that meant that the -- the medicine started to fail its dissolution test and became ineffective. Abbott had to recall it at the cost of hundreds of millions of dollars and reformulate before they could get it back to market.

Q. Were there methods described in the prior art about how to determine whether a pharmaceutical salt exists in multiple crystalline forms?

A. Yes. There were.

Q. And could you describe those briefly?

A. Yes. Typically polymorphism screening is the way it's done. Very similar to salt screening, except there's no need to choose a salt. It's a case of trying to crystallize the drug substance under a representative range of conditions in order to see what crystalline forms result if it's crystallized in different ways.

Q. In pharmaceutical development, how often are drugs under development subjected to crystalline polymorph screening?

A. These days, pretty much all the time.

Q. Thank you for that technical background, Dr. Steed. Let's --

THE COURT: So, Mr. Cooper, if you're going on to something else, why don't we take our morning break here. Okay?

MR. COOPER: Yes, sir.

10:26:37 THE COURT: So, we'll have a 15-minute break. We'll be in recess.

10:26:41 DEPUTY CLERK: All rise.

10:27:19 (Recess was taken.)

10:39:47 DEPUTY CLERK: All rise.

10:39:50 THE COURT: All right. Everyone be seated.

10:39:52 Let's continue.

10:39:58 BY MR. COOPER:

10:40:03 Q. Now, Doctor, the last question I asked you before the break was about how often drugs under development are subjected to crystalline polymorph screening, and your answer referred to nowadays.

10:40:16 Could you describe how often drugs were -- under development were suggested to crystalline polymorph screening as of the priority date?

10:40:24 A. Also, essentially all of the time.

10:40:29 Q. All right.

10:40:29 MR. COOPER: And now we're on DDX Steed 14. And let's turn to the next part of your testimony on written description.

10:40:35 BY MR. COOPER:

10:40:36 Q. In forming your opinions on written description, did you apply your understanding of the applicable legal standard?

10:40:42 A. I did. Yes.

MR. COOPER: Let's move to DDX Steed 15.

BY MR. COOPER:

Q. Does this slide summarize the written description standard that you applied to your analysis?

A. It does, yes.

MR. COOPER: Let's go to DDX Steed Slide 16.

BY MR. COOPER:

Q. And first let's provide just a brief overview. In your opinion, did the inventors possess and disclose the full scope of the asserted claims of the malate salt patents with sufficient written description?

A. No. They did not.

Q. What is the relevant genus for your written description analysis?

A. Yes, so the '439 patent claims cover any crystalline cabozantinib (L)-malate salt.

Q. How many different crystalline cabozantinib (L)-malate salts are there?

A. We know of 11 at the moment, but it's a potentially infinite genus because there could be another one discovered in the future or, indeed, many discovered in the future.

Q. In your opinion, what species of crystalline cabozantinib (L)-malate salts did Exelixis possess and disclose in the malate salt patents?

A. They possessed and disclosed two, two closely related

forms, the N-1 and the N-2 forms.
Q. Would a POSA understand that N-1 and N-2 are representative of the full scope of crystalline cabozantinib (L)-malate salts?
A. No. They wouldn't understand that. As I testified, each solid form has its own unique set of properties. N-1 and N-2 are just two of those solid forms and actually happen to be quite closely related to each other. So they don't cover the full scope of solid form properties.
Q. Does the specification of the malate salt patents provide any data disclosing the crystalline cabozantinib (L)-malate salts that the inventors possessed?
A. It does, yes.
MR. COOPER: Let's go to DDX Steed Slide 17.
BY MR. COOPER:
Q. What have you excerpted from JTX-1, the '439 patent, on this slide?
A. Yes. So here I'm showing various figures from the '439 patent that contain characterization data for the two forms that Exelixis did possess and did describe.
Q. Can you describe what the data is that you've pulled from Figure 1 and Figure 8?
A. Yes, Figure 1 and Figure 8 are the X-ray powder diffraction patterns that respectively form N-1 and form N-2. They're distinct from each other even though they do

10:42:57 have some similarities, and they identify these as having two different underlying crystal structures.
10:43:02 Q. But what do Figures 5 and 12 show?
10:43:04 A. That's the thermogravimetric analysis data. It shows how each of those two forms changes its weight according to -- according to temperature, and these particular cases, they don't change weight up to a certain decomposition point, and that means they're non-solvated forms.
10:43:20 Q. What do Figures 6 and 13 show?
10:43:23 A. These are the DSC, differential scanning calorimetry traces. They're a way of measuring melting point, and these two have similar but not identical melting points.
10:43:33 Q. What do Figures 7 and 14 show?
10:43:34 A. This is analytical technique called moisture absorption. It tells a person of skill how these two solid forms change -- change their mass as a function of relative humidity, so in other words, whether they absorb moisture or not.
10:43:49 MR. COOPER: Let's go to DDX Slide 18.
10:43:49 BY MR. COOPER:
10:43:53 Q. What are you showing on this slide?
10:43:54 A. So these are two other Exelixis patents, the '776 and '549 patents which claim specifically the N-1 and N-2 forms.
10:44:05 Q. How does the specification of the malate salt patents compare to the specification of the '776 and '549 patents?

10:44:14 A. It's the same specification. They're in the same patent family.

10:44:17 Q. And for the record, what is JTX-9 in your binder that is referenced on the slide?

10:44:21 A. That's the '776 patent which the claims are directed to the N-2 crystalline form.

10:44:27 Q. When did the '776 patent issue?

10:44:30 A. It was November the 4th, 2014.

10:44:33 Q. What is JTX-10?

10:44:35 A. That's the '549 patent that claims the N-1 form, and that issued on November 7th, 2017.

10:44:41 Q. In reviewing Exelixis' documents during your work on this case, did you see any evidence that the inventors ever possessed any crystalline cabozantinib malate salts other than N-1 and N-2?

10:44:52 A. I did not see any evidence to that effect, no, and, in fact, they stated that they did not possess any other forms.

10:44:58 MR. COOPER: Can we pull up DDX-20?

10:44:58 BY MR. COOPER:

10:45:04 Q. Dr. Steed, what is this exhibit?

10:45:05 A. This is an extract from Exelixis' NDA for cabozantinib malate.

10:45:11 Q. When did Exelixis submitted their NDA for cabozantinib tablets?

A. I believe it was 2015.

MR. COOPER: Let's go to Page 2 of the exhibit and call out Section 3.4.

BY MR. COOPER:

Q. What is Exelixis reporting to FDA in their NDA submission?

A. Here they tell FDA that cabozantinib (S)-malate -- that's the same as (L)-malate -- was found to exist in two neat -- that's what the N stands for -- closely related crystalline solid forms, N-1 and N-2, that have similar properties. They go on to say that they undertook both a manual and a high throughput crystallization polymorph screen and no other forms were identified in those studies.

Q. Are there additional crystalline cabozantinib (L)-malates that are known to exist?

A. Yes, there's at least nine more now.

MR. COOPER: Let's go to DDX Steed Slide 19.

BY MR. COOPER:

Q. What are you slowing on this slide?

A. Yes. So these are other patent or patent application documents reporting those other nine forms that I was alluding to.

Q. What is DTX-333?

A. That is MSN's '160 patent that covers MSN's form S.

Q. What are PTX-256 and DTX-222?

A. These are two Mylan patent documents that report Mylan form M-1 through M-4.

Q. What is DTX-121?

A. It's a Cipla -- Cipla PCT document reporting Cipla's form C-2 through C-5, so an additional four forms.

Q. Was the MSN, Mylan and Cipla patent literature published by October 2020?

A. Yes, it was.

Q. Does the patent literature report on unique characteristics of the different crystalline cabozantinib (L)-malate salts?

A. Yes, the properties of each are described.

MR. COOPER: Let's go to DDX Steed Slide 20.

BY MR. COOPER:

Q. Could you explain, what are you showing on the left-hand part of this slide?

A. Yes, so these are four example powder diffraction patterns of the total 11 forms that I was just talking about, N-2 shown in red. And I've got an example Mylan, an example Cipla, and MSN's form S powder diffraction patterns are shown on the left-hand side there. And they're all distinct patterns that identify these as different crystalline forms.

Q. And specifically you've put on the Slide M-4 and C-4; is that right?

A. That's right, yes.

Q. What are you showing on the right-hand part of this slide?

A. These are claimed peak positions for those various forms that have been measured from these experimental X-ray powder diffraction patterns. These are not all the peaks, but they are the ones that the various patent inventors chose to claim as being unique sets of peaks that identify their invention.

Q. And it looks like if you compare any one reported crystalline form against another, there are some overlapping XRPD peaks. How does that affect your opinion?

A. Yes, it doesn't affect my opinion. It's quite normal that there will be some peaks that overlap from one diffraction pattern to another. If you have a look at these diffraction patterns, there are many peaks there. And so, it's not surprising that by coincidence some peaks may be kind of -- may be in similar positions in -- in more than one form. That doesn't change the fact that the overall patents are different indicating they're different solid forms, and if you take the claimed peak positions as a set, each set uniquely identifies a polymorphic form.

Q. Now, you've placed a few examples on this slide. But did you review and draw any conclusions about whether the crystalline structure of all 11 of the cabozantinib

(L)-malate salts identified in the patent literature were unique?

A. I did. I reviewed the data for all 11 forms, and it's my opinion there are 11 different forms.

Q. Does the Mylan, Cipla and MSN patent literature provide any information about how each of their different crystalline cabozantinib (L)-malate salts were prepared?

A. Yes. Each document has a recipe by which it's particular forms are made.

MR. COOPER: Let's go to DDX Steed Slide 21.

BY MR. COOPER:

Q. What have you placed in each of the three columns on this slide?

A. So these are three examples of those kinds of procedures, typically exemplified by examples within the patent documents. So, here I'm showing just for illustration the fact that different solid forms are made in different ways. The recipe for Exelixis' form N-2, MSN's form S and Cipla's form C-4.

Q. What are some of the differences in the way that they are made that you have highlighted on this slide?

A. Yes. So the solid form that comes out depends upon the circumstances under which it crystallizes, and there are a number of different possible ways you can crystallize. I'm highlighting, for example, for Exelixis' form N-2 in

10:50:03 purple there that they use seed crystals to select form N-2 and stop other forms from being produced. That's not used by the other methods.
10:50:12 Q. What are you highlighting in blue on this slide?
10:50:14 A. MSN's form S uses an antisolvent called dichloromethane which the other forms don't use so they add that near to the crystallization stage and that -- and so the form S precipitates from this dichloromethane solution.
10:50:31 Q. What are you highlighting in green on this slide?
10:50:33 A. So, the other procedures use some different solvents. So, form N-2 and form S further up the procedure use a solvent called tetrahydrofuran, and N-2 uses other solvents as well, like isobutyl ketone. Cipla's form C-4 uses a rather different kind of solvent. That's dimethyl carbonate and heptane.
10:50:54 Q. What are you highlighting in orange on this slide?
10:50:56 A. Again, further differences is the amount of water added between form S and form C-4. 70 ml added in form S and just a very small amount of water for C-4, just 50 microliters. And these are just examples of other differences that are in these various preparation procedures, different temperatures, different slurrying times, different crystallization times and so on.
10:51:20 Q. And have you reviewed all of the processes for the 11 crystalline cabozantinib (L)-malate forms and found them to

10:51:27 be unique?
10:51:28 A. I have, yes. Each is crystallized in a different
10:51:30 way, as you'd expect because they're different forms.
10:51:33 Q. Doctor, is there any doubt that crystalline
10:51:36 cabozantinib (L)-malate salts exist that the malate salt
10:51:39 patent inventors did not possess at the priority date?
10:51:42 A. No, there's no doubt at all. And, in fact, last time
10:51:45 we were here, Your Honor, you ruled that MSN's form S
10:51:47 doesn't infringe the form N-2 patent and so it's a different
10:51:50 form.
10:51:51 Q. Now, even at the priority date when the Mylan Cipla
10:51:54 and MSN patent literature was not available, what would a
10:51:58 POSA have reasonably expected about the whether there were
10:52:01 crystalline cabozantinib (L)-malate salts other than N-1 and
10:52:05 N-2?
10:52:05 A. Yes. It was the Paulekuhn document demonstrating
10:52:09 polymorphism was well-known at the priority date. So even
10:52:12 if there were no other polymorphs known, a person would have
10:52:14 a strong reason to expect that the other polymorphs may be
10:52:18 discovered in the future.
10:52:19 Q. Based on the data you reviewed, is the crystalline
10:52:22 structure of N-1 and N-2 representative of the crystalline
10:52:26 structure of other crystalline cabozantinib (L)-malate salts
10:52:30 that exist or that could reasonably be expected by a POSA to
10:52:34 exist?

A. No, each one has its own unique powder diffraction pattern. N-1 and N-2 are actually quite similar to each other, and they're different to many of the other powder diffraction patents that I've reviewed.

And so, of course, by definition, each solid form is -- is a different solid form with a different structure. And N-1 and N-2 aren't representative of the other forms we know of, and likely not any that will be discovered in the future.

Q. Does the specification of the malate salt patents provide information about properties of N-1 and N-2 other than the crystalline structure?

A. Yes, it does.

MR. COOPER: Let's pull up JTX-1. And go to Page 36 and call out Column 6, Line 56.

Over to Page 7, Column 7, Line 9.

BY MR. COOPER:

Q. Doctor, what does Exelixis' specification report about the benefit of the properties of crystalline cabozantinib (L)-malate salts, also referred to as Compound I, in the disclosed -- in the patent compared to other salts of cabozantinib and cabozantinib free base?

A. They speak of their properties, and in general they say that the N-1 and N-2 forms have improved properties over other salt forms.

Q. What does the specification say about the scope of the disclosure with respect to specific crystalline forms like N-2?

A. They make it clear that they're using the names of polymorphs, like N-2, to indicate a material with a particular set of properties. And so, they're saying here that if something has the same properties, then they don't determine the name to be limiting, that would also be regarded as N-2.

And, of course, the converse is true, that if something has very different properties, that wouldn't be form N-2.

Q. Would a POSA expect other crystalline cabozantinib malate salts to have similar or identical physical and chemical characteristics as N-1 and N-2?

A. No. If there were similar or identical physical chemical characteristics, that would make it N-2 or N-1. If the characteristics are different, then it's a different form.

MR. COOPER: Let's go to Page 49 and call out Column 31, Lines 5 through 15.

BY MR. COOPER:

Q. What property is identified in the specification here?

A. So here, the specification is talking about the

differential scanning calorimetry thermogram as a way of measuring melting point for Forms N-1 and N-2.

Q. What does it report about the melting point of N-1 and N-2?

A. For form N-1, it gets 187 degrees C, 186 for N-2. So in this case, they're really quite similar to each other.

Q. Would a POSA expect other crystalline cabozantinib (L)-malate salts to have the same melting point?

A. No, each one will have its own melting point. It might be similar, but more likely to be quite different because it's a unique property of a particular form.

MR. COOPER: Let's pull up DTX-222, which is the Mylan patent application. And go to Page 36 and call out Figure 9.

BY MR. COOPER:

Q. What characteristic does this figure show?

A. So, here's a differential scanning calorimetry trace for Mylan's form M-4. This has a lower melting point of a 174.87. And, of course, MSN's form S is even lower than that, at 113.

MR. COOPER: Let's go back to the '439 patent, JTX-1, and go to Page 37. Can we call out Column 7, Lines 10 through 18.

BY MR. COOPER:

Q. What property of the crystalline cabozantinib

(L)-malate salts disclosed in the patent is identified here?
A. So, again, the inventors are still talking about their combination of pharmaceutical properties. Here, they're referring to the TGA properties. And they say that no solvent loss was observed for forms N-1 and N-2. So that indicates they're non-solvated forms.
Q. What does -- okay. Thank you.
Would a POSA expect other crystalline cabozantinib (L)-malate salts to show no solvent loss in a TGA experiment?
A. No. If it was a solvated crystalline form that had solvent molecules as a regular part of the -- of the crystal lattice then the TGA would show that by virtue of a mass loss as the temperature was increased.
MR. COOPER: Let's pull up DTX-222 and go to Page 30 and call out Figure 3.
BY MR. COOPER:
Q. What characteristics does this figure show?
A. So this is the thermogravimetric trace of Mylan's form M-1. And you can see the mass loss of 4.260 percent highlighted there occurring between room temperature and about 125 degrees C. That indicates solvent molecules coming off form M-1. So that's a solvated crystalline form.
MR. COOPER: Let's go back to the '439 patent, JTX-1. And go to Page 37 and call out Table 1 and Column 7.

And the entry for (L)-malate in Column 8.
BY MR. COOPER:
Q. What does Table 1 in the patent report on?
A. Table 1 is a further listing of properties of the -- of the forms N-1 and N-2. In this case, the malate salt.
Q. What is -- what is one of the properties of the crystalline cabozantinib (L)-malate salt disclosed in the patent here?
A. The crystalline malate salts are -- of the patent are said to be nonhygroscopic.
Q. Would a POSA expect other crystalline cabozantinib (L)-malate salts to be nonhygroscopic?
A. No. Like the other properties, hygroscopicity is an intrinsic property of a particular form. MSN's form S happens to be hygroscopic.
Q. What other property of the crystalline cabozantinib (L)-malate salts had been disclosed in the patent as identified here?
A. This table also lists the property of solubility measured in number of milligrams per milliliter. And the (L)-malate salts have a solubility of 0.059.
Q. Would a POSA expect other crystalline cabozantinib (L)-malate salts to have the same solubility?
A. No. Solubility is another one of those intrinsic properties of a form that will be different for each form.

Q. Based on the data you have reviewed, are the properties of the N-1 and N-2 representative of the properties of other crystalline cabozantinib (L)-malate salts that exist, that are known to exist, or would be expected to exist by a POSA?
A. No. They're not representative.
Q. And even if the Mylan, Cipla, and MSN patent literature was not available at the priority date, would a POSA have expected N-1 and N-2 to have the same or similar properties as other crystalline cabozantinib (L)-malate salts?
A. No, they wouldn't. If the properties were the same, it wouldn't be a different form. So they would expect the properties to be different.
Q. All right. Thank you, Doctor.
MR. COOPER: Let's move to DDX Steed 22.
BY MR. COOPER:
Q. And turn to the next part of your testimony on obviousness --
THE COURT: Actually, before we do that.
Dr. Steed, would you -- in terms of your understanding of when the word "representative" is being used to describe different polymorphs, is N-1 representative of N-2?
THE WITNESS: That's a really good question.

They are slightly different to each other. So, I would say even those two are distinct from each other, or otherwise they would be the same form. But they have quite similar properties.

THE COURT: Well -- and I guess the point that I'm wondering about is whether essentially your view is that, as a practical matter, no polymorph is going to be representative of another polymorph?

THE WITNESS: It's an interesting question. I mean, I wouldn't necessarily say that possession of -- of form N-1 and N-2, for example, would indicate also possession of form N-1. So, because each polymorph is unique, then I suppose each one is only representative of itself, would be my opinion.

THE COURT: All right. Go ahead.

Thank you, Doctor.

THE WITNESS: Thank you.

MR. COOPER: Let's move to DDX-12 -- 22.

BY MR. COOPER:

Q. In forming your opinions, did you apply your understanding of the applicable legal standard?

A. I did.

MR. COOPER: Let's move to DDX Steed 23.

BY MR. COOPER:

Q. Does this slide summarize the obviousness-type double

patenting standard that you applied to your analysis?

A. It does, yes.

MR. COOPER: Let's pull up DTX-13.

BY MR. COOPER:

Q. Dr. Steed, what is this exhibit?

A. This is the '473 patent that we've heard of already today.

Q. When did the '473 patent issue?

A. That's August 25th, 2009.

Q. Who is the assignee of the '473 patent?

A. Exelixis.

Q. Doctor, did you consider whether the asserted claims of the malate salt patents are rendered obvious over any claims of the '473 patent under the obviousness-type double patenting doctrine?

A. I did. Yes.

MR. COOPER: Let's go to DDX Steed 24.

BY MR. COOPER:

Q. Now, what are you showing on the left-hand side of this slide?

A. This is Claim 5 of the '473 patent, which is my reference claim.

Q. When does the '473 patent expire?

A. 2026.

Q. On the right-hand side, you've reproduced again the

asserted claims of the malate salt patents. When do those expire?

A. 2030.

Q. Is there an element of the '473 patent Claim 5 and the asserted claims of the malate salt patents that you've highlighted in green on this slide?

A. Yes. We've seen it quite a few times now. That's the chemical structure of the cabozantinib molecule.

Q. Was the cabozantinib molecule also disclosed in the prior art?

A. Yes, it was in the priority application that underlies the '473 patent.

Q. So, is the cabozantinib molecule a patentably distinct element between the two?

A. No, it isn't. It's called out by structure in Claim 5 and -- and by name in the malate salt patents, but it's the same thing.

Q. Is there an element of the '473 patent Claim 5 and the asserted claims of the malate salt patents that you've highlighted in yellow?

A. Yes. Claim 5 of the '473 is also directed towards the pharmaceutically acceptable salts -- the genus of pharmaceutically acceptable salts of cabozantinib.

Q. Is crystalline (L)-malate a pharmaceutically acceptable salt of cabozantinib?

A. Yes, it is.
Q. So, in your opinion, does the genus of pharmaceutically acceptable salts claimed in the '473 patent include the species of crystalline (L)-malate salts claimed in the malate salt patents?
A. Yes, it does.
Q. Are there any reasons a POSA would have been motivated to prepare the (L)-malate salt specifically with a reasonable expectation of success in being able to do so?
A. Yes, there is.
MR. COOPER: Let's go to DDX Steed 25.
BY MR. COOPER:
Q. Now, have you listed those considerations on this slide?
A. Yes, these are the considerations that a person of skill would be looking at in running one of those routine and customary salt screens as applied to cabozantinib -- as applied malate.
Q. What is the first consideration about (L)-malic acid that you've identified?
A. Yes. A person of skill would look to the prior art in order to see which kinds of counterions had been used in FDA approved drugs previously.
Q. Are malic acid and malate identified in the list of FDA approved and commonly used counterions in API salts that

were in the prior art lists that you previously discussed?

A. Yes, they are. They were in all the ones that I showed.

Q. How would a POSA rely on those prior art lists in performing a salt screening?

A. That would be a starting point for them to -- to go about their choice of -- of acid in this case.

Q. Were there any FDA approved malate salts in the prior art that would have been notable to a POSA?

A. Yes. There's another tyrosine kinase inhibitor, sunitinib, which is also formulated as an (L)-malate salt. It's a different molecule, doesn't have the same chemical structure but it would indicate that (L)-malate is a suitable ion for this type -- kind of drug.

Q. What is the second consideration you've listed?

A. Obviously for administration to humans, you would need it to be non-toxic. So a person of skill would look to non-toxic acids in their counterions and safe -- safe for consumption.

Q. What did the prior art report with respect to the toxicity of malic acid?

A. Malic acid is very much non-toxic. It's a natural product. It comes from fruits, sometimes called apple acid.

MR. COOPER: Let's pull up DTX-167.

BY MR. COOPER:

Q. What is this exhibit?
A. This is a prior art reference from the -- entitled *Encyclopedia of Pharmaceutical Technology*, edited by Swarbrick.
Q. And did you rely on a chapter in this textbook by Bighley?
A. I did, yes.
Q. Does this reference contain one of the lists of FDA approved pharmaceutically acceptable salts that you've previously discussed?
A. It does, yes.
MR. COOPER: Let's go to Page 36 and call out the second paragraph with the heading "Preparation of organic salts."
BY MR. COOPER:
Q. Does the Bighley reference disclose a preference for any of the anions from the list of FDA approved salts that are identified in this chapter?
A. Yes. Bighley alludes to some problems that can be encountered with mineral acid salts, like hydrochlorides, and says that many of the problems can be avoided by choosing a hydroxylated conjugate acid with a pK_a of about 3 to 4. And then Bighley goes on to list, I think, about 12 possible candidate ions, so that includes formate, acetate, glycolate, lactate, malate, gluconate, tartrate, citrate,

succinate, malonate, fumarate, and maleate.

MR. COOPER: Let's go back to DDX-25.

BY MR. COOPER:

Q. What is the third consideration about (L)-malic acid that you've listed?

A. Yes. And I should have said Bighley indicates those are all -- those are non-toxic options, as I was alluding to.

In addition to that, of course, as I was saying when I was talking about pK_a, the acid has to be acidic enough in order to actually form a salt with a base like cabozantinib and that's the pK_a Rule-of-2.

Q. Is the pK_a of cabozantinib reported in the prior art?

A. It isn't, no, but it's readily measured by titration.

Q. Is the pK_a of malic acid and other commonly used counterions reported in the prior art?

A. Yes, it is. It's about 3.4.

Q. In forming your opinions, did you consider which pharmaceutically acceptable anions from the FDA approved list would meet the Rule-of-2 for cabozantinib?

A. Yes, I did.

Q. Did you also consider any references introduced by Dr. Trout that identified the pharmaceutically acceptable anions that would meet the Rule-of-2 for cabozantinib?

A. Yes. In addition to the list that I looked at,

11:07:26 Dr. Trout also mentioned an article by Stahl that has similar kinds of lists in it handedly ranked by pK_a.

11:07:33 MR. COOPER: Let's go to PTX-610.

11:07:33 BY MR. COOPER:

11:07:37 Q. Dr. Steed, what is this exhibit?

11:07:38 A. This is that Stahl reference. It's from *Handbook of Pharmaceutical Salts*, first author Stahl; it's a prior arts reference.

11:07:46 MR. COOPER: Let's go to Page 338 to 339, and call out Table 2 on those two pages.

11:07:49 BY MR. COOPER:

11:07:52 Q. And what is provided in Table 2 of the Stahl reference?

11:07:55 A. So this is a list of pharmaceutically acceptable acids that can be used to make salts as acid addition salts and they're ranked in order of increasing pK_a value, so decreasing acidity.

11:08:08 Q. Did both -- did you consider how many of the acids in this list that Dr. Trout identified would meet the Rule-of-2 for cabozantinib?

11:08:16 A. Yes, I did.

11:08:19 MR. COOPER: Let's underline D, the lactic acid in the second column.

11:08:22 BY MR. COOPER:

11:08:23 Q. What is the significance of this acid?

11:08:25 A. So, the red line, which finishes at lactic acid, is where the Tong Rule-of-2 cuts off. So, anything above the red line would be acidic enough under Tong's Rule-of-2 to form a salt with cabozantinib.

11:08:40 MR. COOPER: Let's call out the row for (L)-malic acid.

11:08:42 BY MR. COOPER:

11:08:44 Q. And what can you see in that row?

11:08:45 A. Yeah. So here's (L)-malic acid, we can see its pK_a value and it has two. But it's the first one that's the important one, 3.459.

11:08:55 Q. And what would a POSA conclude in evaluating these anions -- I'm sorry. Strike that.

11:09:02 Is there any other information presented in this list that a POSA would consider in selecting a counterion?

11:09:09 A. Yes. And I think it's not quite been called on there, but it also has a final column of GRAS status. And if you extend the -- the yellow a little bit, then you'll see a plus in GRAS status.

11:09:20 Q. And what significance would a POSA place on GRAS status?

11:09:24 A. So the GRAS status is the FDA's -- thank you -- is the FDA's generally recognized as safe for administration to humans. So obviously if something is GRAS status, then it's -- if you like preapproved for the use in something

that a human would consume and that's a desirable property.
Q. And how many acids in the Stahl list meet the Tong Rule-of-2 and are identified as GRAS?
A. Including malic acid, it's nine.
Q. And you said those are indicated by a plus?
A. That's right.
Q. Is malic acid one of the acids designed and designated as GRAS?
A. It is.
Q. And so, did you consider the relative scope of previously used pharmaceutically acceptable counterions that would meet the Rule-of-2 for cabozantinib from your list that you identified previously, as well as this list from Dr. Trout and as -- strike that.
Did you consider the relative scope of previously used pharmaceutically acceptable counterions that would meet the Rule-of-2 for cabozantinib and were recognized as non-toxic and safe in your analysis?
A. I did, yes. It's a relatively limited list, the sort that could be easily encompassed by a routine and customary salt screen.
MR. COOPER: Let's go to DDX Steed 26.
BY MR. COOPER:
Q. You also mentioned structural compatibility as a consideration. What would a POSA understand in that regard

based on the chemical structures of cabozantinib and (L)-malic acid that were disclosed in the prior art?

A. Yes. As I just -- as I described, crystalline salts are desirable and a POSA would look to their knowledge of the kinds of interactions between the anion and the counterion of the salt that might make for a stable crystal, and I'm showing one of those kinds of interactions here between cabozantinib and malate. This image is taken from the crystal structure of the N-1 form, but the interaction notated in yellow would -- would be one that would be well-known to somebody like myself who knows about crystal interactions.

So, what I'm showing here is that in all salts, there will be a positive to negative attraction, that's the lower of the two dotted lines. It's a strong hydrogen bonding interaction. Many salts will have that kind of strength.

But in addition in the case of a quinoline derivative like this, and carboxylate like malate, we've got a second interaction to give us an eight-atom hydrogen bonded ring. And this is a reproducible motif, it's called a supramolecular synthon parlance and a person of skill would be aware that this kind of interaction would be a stabilizing interaction in crystals of this type with malate.

Q. And so what would a POSA conclude about cabozantinib and (L)-malic acid in evaluating their structural compatibility?
A. That they would be -- they would be -- I strongly suspect that they would be likely to form a stable crystal.
MR. COOPER: Okay. Thank you. You can take that down.
BY MR. COOPER:
Q. Now, based on a POSA's general knowledge and the prior art that you've discussed, what is your opinion about whether a POSA would have been motivated and found it obvious to prepare the (L)-malate salt of cabozantinib with a reasonable expectation of success?
A. Yes. I think malate is a strong candidate for inclusion in that salt screening process that I alluded to. And following the routine and customary path, a person of skill would arrive at cabozantinib (L)-malate without invention be able to analyze its properties.
Q. Would a POSA be further motivated to prepare a crystalline form of cabozantinib (L)-malate with a reasonable expectation of success in being able to do so?
A. Yes. As I alluded to, more than 90 percent of pharmaceuticals are in crystalline form. Crystalline forms have desirable properties, such as greater stability, less hygroscopicity, and so the crystalline form would be the

go-to form.
Q. Is there anything in the prior art that would teach away from a POSA preparing the crystalline (L)-malate salt of cabozantinib?
A. No.
Q. Now, to sum up, in your opinion are there any patentably distinct differences between Claim 5 of the '473 patent and the asserted claim of the '439 patent?
A. No. I don't think there are.
MR. COOPER: Let's go to DDX Steed 27.
BY MR. COOPER:
Q. And turning to the '440 patent, are there any additional limitations of that patent that are not in the '439 patent?
A. Yes. In addition the '440 patent requires a pharmaceutical composition.
Q. Does the '440 patent specification anywhere identify a specific pharmaceutical composition containing cabozantinib (L)-malate or how to make one?
A. No, it doesn't. It just refers to pharmaceutical compositions in general.
Q. Did the prior art disclose pharmaceutical compositions of cabozantinib (L)-malate?
A. Yes, it did.
MR. COOPER: Let's pull up DTX-180.

Q. Dr. Steed, what is this exhibit composition?
A. So this is the '928 application that underlies that '473 patent.
Q. When was the '928 application published?
A. March the 8th, 2007.
Q. Under "related applications data," it states that "The '928 publication is a continuation of an international PCT number U.S. 04/31523."
Do you see that?
A. I do.
Q. And the title of the '928 application refers to c-Met modulators. What is your understanding of what those are?
A. So these are anti-cancer drug, specifically tyrosine kinase inhibitors.
MR. COOPER: Let's go to Page 314 of this exhibit and call out Claim 105. And then also call out from Page 317, entry 12.
BY MR. COOPER:
Q. What is this compound claimed here in the '928 application?
A. This is cabozantinib.
MR. COOPER: Let's pull up Page 145 of the exhibit and call out Paragraph 297.
BY MR. COOPER:
Q. What does the '928 application disclose regarding

administration of the compounds that are claimed in the reference?

A. Yes. Exelixis '928 teaches administration of the compounds of the invention or their pharmaceutically acceptable salts which would include the malate salt in appropriate pharmaceutical compositions.

Q. Does the '928 publication identify any specific pharmaceutical compositions with cabozantinib or how to make one?

A. No, it doesn't in the same way as the '440 patent doesn't. It just talks about them in general.

Q. Based on a POSA's general knowledge and the prior art you've discussed, what is your opinion about whether a POSA would have been motivated and found it obvious to prepare a pharmaceutical composition of that crystalline (L)-malate salt that you've discussed?

A. I believe they would have been motivated to produce a pharmaceutical composition and found it obvious and not patentably distinct from Claim 5 of the -- of the reference patent.

MR. COOPER: Let's go to DDX Steed 28, turning to the '015 patent.

BY MR. COOPER:

Q. Are there any additional limitations of that patent that are not in the '439 patent?

A. Yes. That has the additional requirements of a method of treating cancer, specifically kidney cancer.

Q. Does the '015 patent anywhere identify any specific methods or other properties of kidney cancer treatment resulting from administering cabozantinib (L)-malate to a patient?

A. No, it doesn't. It just talks in general of treating cancer and specifically kidney cancer.

Q. Did the prior art disclose the use of cabozantinib to treat kidney cancer?

A. Yes, it does in that '928 application once more.

MR. COOPER: Let's pull up the '928 application, DTX-180, and go to Pages 4 through 5 and call out Paragraph 31.

BY MR. COOPER:

Q. What does the '928 publication disclose here?

A. Yes. It's talking about treating diseases associated with the abnormal and/or unregulated Cellular activities, specifically cancer.

Q. And does the '928 application identify the types or scopes of cancer that claimed compounds treat?

A. It does, yes.

MR. COOPER: Let's go to Page 143 and call out Paragraph 285.

BY MR. COOPER:

11:17:39 Q. Is kidney cancer identified in this definition of cancer?
11:17:43 A. It is, yes. It specifically calls out kidney cancer.
11:17:48 Q. Now, does the '928 publication identify any specific methods or other properties of kidney cancer treatment resulting from administering any of the claimed compounds to a patient?
11:17:58 A. No, it just talks about it in general in just the same way as the '015 patent does.
11:18:04 Q. Based on a POSA's general knowledge and the prior art that you've discussed, what is your opinion about whether a POSA would have been motivated and found it obvious to use the crystalline cabozantinib (L)-malate salt that you've discussed to treat kidney cancer?
11:18:18 A. I believe they would have been motivated and would have found it obvious.
11:18:23 Q. And in your opinion, does the treatment of kidney cancer element make the asserted claim of the '015 patent patentably distinct over Claim 5 of the '473 patent?
11:18:32 A. No. I don't think it does.
11:18:36 MR. COOPER: Thank you. You can take that down.
11:18:36 BY MR. COOPER:
11:18:37 Q. Doctor, as part of your analysis, did you also consider purported objective indicia?
11:18:43 A. I did.

Q. We expect to hear from Exelixis about certain of those. But while we have you on the stand today, let's briefly discuss your opinions with what we expect Exelixis to assert.

Now, in forming your opinions, did you apply your understanding of the applicable legal standard of unexpected results?

A. I did.

MR. COOPER: Let's go to DDX Steed 29.

BY MR. COOPER:

Q. Is your understanding of that standard summarized on this slide?

A. It is. Yes.

MR. COOPER: Thank you. You can take that down.

BY MR. COOPER:

Q. Do you understand that Exelixis' expert has asserted that it was unexpected that the (L)-malate salt of cabozantinib was found to be the preferred salt for development?

A. I do understand that. Yes. But I don't agree with it.

Q. Why not?

A. Well, in order to have an expectation that's -- in order to -- in order for it to be unexpected, you would have to have an expectation that it wouldn't work. And as I've

11:19:42 described the routine and customary salt screening process, you simply select the acids and then put them through that process. So, you wouldn't expect a given acid to not work. You would just apply the routine customary process.

11:19:53 Q. Do you understand that Exelixis' expert has also asserted that crystalline cabozantinib (L)-malate exhibited unexpectedly superior dissolution compared with amorphous cabozantinib (L)-malate?

11:20:06 A. Yes, I've heard that, and I also don't agree with that.

11:20:09 Q. Why is that?

11:20:10 A. There's nothing unexpected about the solubility of crystalline cabozantinib (L)-malate. It's the amorphous that's weird here. Amorphous cabozantinib (L)-malate is quite hygroscopic and it forms clumps. So it dissolves very quickly. And so it is true that the crystalline form dissolves faster than the amorphous, but that's because the amorphous is anomalous, it dissolves unexpectedly slowly, not because the crystalline is unique in that way.

11:20:36 Q. And is amorphous cabozantinib (L)-malate covered by any of the asserted claims?

11:20:41 A. No.

11:20:44 Q. One final point on objective indicia, and it's related to the blocking patent opinion that we will hear from Dr. McDuff.

MR. COOPER: Let's pull up DTX-192.

BY MR. COOPER:

Q. Dr. Steed, what is this exhibit?

A. This is the '140 patent application that we've seen earlier today.

Q. And the '140 publication issued from the international 31523 application. Do you see that?

A. I do. Yes.

Q. Is this exhibit in the same patent family as the '928 publication and '473 patent we looked at previously?

A. It is, yes.

Q. In your opinion -- and have you reviewed this exhibit?

A. I have.

Q. In your opinion, does the subject matter claimed by the malate salt patents lie within the scope of the WO '140 publication and the '473 patent, which we've already looked at?

A. Yes, it does.

Q. From a scientific perspective, would a POSA have been discouraged from developing compositions comprising a claimed crystalline cabozantinib (L)-malate salt after the publications of the '140 publication and '473 patent?

A. Yes, they would have done it. It would discourage them from adopting, of developing the kind of technology

that's covered by this patent application just in case the application was granted and then they would infringe claims.

Q. And we will hear from them later, but did you consider the opinions and rely on any of MSN's other experts regarding objective indicia asserted by Exelixis in reaching your opinions in this case?

A. Yes, I considered the opinions of Dr. Mega and Dr. McDuff.

Q. Dr. Steed, in your opinion, do objective indicia support a finding that the asserted claims of the malate salt patents are not rendered obvious over any claims of the '473 patent under the obviousness-type double patenting doctrine?

A. They do not.

MR. COOPER: All right. Thank you, Dr. Steed. We may hear from you again in rebuttal, but that may address all of your opinions on objective indicia.

I pass the witness at this time.

THE COURT: All right. Thank you, Mr. Cooper.

THE WITNESS: Thank you.

MR. PRUSSIA: Your Honor, may I proceed.

THE COURT: Yes.

CROSS-EXAMINATION

BY MR. PRUSSIA:

Q. You are not a formulator; correct?

A. That's correct.
Q. You don't personally formulate drug products; correct?
A. That's correct.
Q. Now, during your direct, you provided a description to the Court about salt screening.
Do you remember that?
A. Yes.
Q. But you do not personally conduct salt screens; correct?
A. To me that's a routine activity that could be outsourced. I certainly make a lot of salts in my research, but I don't do a salt screen in that kind of way.
Q. My question was correct, you do not personally conduct salt screens; correct?
A. That's right.
Q. Now, consulting with a pharmaceutical drug company to identify the correct salt form for a particular drug substance, that's outside your typical work; right?
A. Yes, I guess that's true.
Q. You can't recall a situation in your entire career where you have made a salt with malic acid; right?
A. Not offhand. I don't think so. I've made many salts. I can't recall if I've made malic acid or not.
Q. And, in fact, you've never made a salt with malic

acid; isn't that true, sir?
A. Not that I can recall offhand.
Q. Now, you're not a medical doctor; right?
A. Correct.
Q. You're not an expert in the clinical treatment of people; right?
A. Correct.
Q. Never designed a clinical trial; right?
A. Yes.
Q. No expertise in treating cancer; right?
A. That's right.
Q. Let's talk about your opinions with respect to obviousness-type double patenting.
MR. PRUSSIA: And if we could have PTX-252. This is Tab 13 in your binder if you need it. It's the '473 patent.
BY MR. PRUSSIA:
Q. Now, during the prosecution of the crystalline malate salt patents, the '473 patent was before the examiner; correct?
A. I can't --
Q. We could help you if you like. Is my question correct, though?
A. I believe so. I'm not -- I'm not sure as I sit here today, but I believe so.

11:25:35 Q. We can help you. If we go to the references cited, about halfway down that column on the left side. Next page. It's Page 3.

11:25:49 That's the '473 patent on the screen; correct?

11:26:06 A. Yes, I believe so.

11:26:07 Q. So the Patent Office allowed -- the Patent Office had the '473 patent during prosecution; correct?

11:26:12 A. That's my understanding.

11:26:13 Q. The Patent Office allowed the claims over the '473 patent; right?

11:26:16 A. Yes.

11:26:17 Q. Now, you understand that obviousness-type double patenting involves comparing the claims of the reference patent to the asserted claims; correct?

11:26:24 A. Correct.

11:26:25 Q. So, let's look at those claims.

11:26:27 MR. PRUSSIA: If we could have Claim 5 on the screen, please.

11:26:29 BY MR. PRUSSIA:

11:26:33 Q. Claim 5 is written in the alternative; correct?

11:26:36 A. You mean in the sense that it has the word "or" in there?

11:26:41 Q. That's exactly right?

11:26:42 A. Yes, that's right.

11:26:43 Q. So my question is correct, that Claim 5 is written in

the alternative; right?
A. Yes, I suppose so.
Q. Claim 5 does not require a salt; correct?
A. I suppose that's true, yes.
Q. Claim 5 allows for just the free base; right?
A. Yes, that's true.
Q. Claim 5 does not identify any particular salt of cabozantinib; right?
A. No.
Q. It doesn't identify any malate salt of cabozantinib correct?
A. That's correct.
Q. It doesn't identify a crystalline salt of cabozantinib; correct?
A. True.
Q. And it doesn't identify a pharmaceutical composition of cabozantinib; correct?
A. That's also true.
Q. And it does not identify a method of treating kidney cancer with cabozantinib; correct?
A. Yes, that's true.
Q. Now, focusing on the language "pharmaceutically acceptable salt thereof," do you see that?
A. I do.
Q. And it's your opinion, as I heard you correct on

11:27:35 direct, it's your opinion that this includes a malate salt; right?
11:27:39 A. Yes. A malate salt would be a species of pharmaceutically acceptable salt.
11:27:43 Q. And that would include a crystalline malate salt, in your opinion; right?
11:27:46 A. Yes.
11:27:46 Q. Now, you were an expert in the first case; right?
11:27:49 A. I was.
11:27:50 Q. And you offered opinions with respect to validity in -- strike that.
11:27:53 You initially offered opinions with respect to validity of the '776 patent in the first case; correct?
11:27:59 A. My memory is hazy, it was a while ago, but I expect that's true.
11:28:03 Q. And you came to trial, you sat in that seat, and you testified to Your Honor with respect to infringement of the '776 patent; correct?
11:28:09 A. Correct.
11:28:09 Q. Now, you never offered an opinion in the first case that this Claim 5 was invalid for lack of written description, did you?
11:28:16 A. Not as far as I recall.
11:28:18 Q. Even though it's your opinion today that this claim covers a crystalline malate salt; correct?

MR. COOPER: Objection; this is outside the scope of direct.

MR. PRUSSIA: It's cross-examination.

THE COURT: Well --

MR. COOPER: I didn't --

THE COURT: So, you know, if he offered an opinion, that's one thing. Not offering an opinion, that's nothing.

MR. PRUSSIA: I'll move on, sir.

BY MR. PRUSSIA:

Q. Now, this patent includes a definition for pharmaceutically acceptable acid addition salts; correct?

A. Can you direct me to that?

MR. PRUSSIA: If we turn to Column 270, Line 15 to 25.

BY MR. PRUSSIA:

Q. It's on the screen as well.

Do you see that?

A. I do.

Q. So the '473 patent includes a definition for pharmaceutically acceptable acid addition salts; correct?

A. I see the words there, yes.

Q. And you did not discuss this definition for pharmaceutically acceptable acid addition salts -- acid addition salts during your testimony on direct; correct?

A. I'm sorry, I'm just reading it. (Witness reviewing.) That's correct.

Q. And this definition expressly lists 24 acids; right?

A. I haven't counted them but I'm sure you're right.

Q. And malic acid is not on that list; right?

A. It's not explicitly on the list but it does say "and the like" at the end.

Q. No -- and we'll get to that. But malic acid is not on the list; right?

A. That's correct.

Q. Now, this patent provides synthetic examples of forming salts; right?

A. I believe so, yes.

Q. And none of the examples of forming salts in the '473 patent describes making a malate salt; correct?

A. To the best of my recollection, I believe that's right.

THE COURT: And, Mr. Prussia, I'm sorry.

MR. PRUSSIA: Yes, Your Honor.

THE COURT: The question a moment ago, did you say it's describing prophetic?

MR. PRUSSIA: Synthetic.

THE COURT: Synthetic.

MR. PRUSSIA: Sorry.

THE COURT: Okay. Thank you.

BY MR. PRUSSIA:
Q. So just to be clear, the '473 patent provides synthetic examples of forming salts; correct?
A. Yes.
Q. And none of those synthetic examples describes making a malate salt; correct?
A. To the best of my recollection, no.
MR. PRUSSIA: And if we turn to Column 324, Example 48, we'll put it on the screen.
BY MR. PRUSSIA:
Q. This is a synthesis of the cabozantinib free base; correct?
A. Yes, it's synthesis of the cabozantinib molecule itself.
Q. And it's the only example in the '473 patent describing the synthesis of cabozantinib; correct?
A. To the best of my recollection.
Q. And it does not describe making any cabozantinib salt at all; right?
A. I don't recall what form it's made into. I guess you were just saying free base. I have no reason to doubt that.
Q. Okay. Now, cabozantinib is not the only compound disclosed in the '473 patent; right?
A. No.
Q. There are hundreds of other compounds exemplified in

the '473 patent; right?
A. Yes, that's my understanding.
Q. Now, for some of those compounds, the '473 patent discloses examples of forming salts; right?
A. Yes, I believe so.
Q. But none of those examples include malate salts; right?
A. Also true.
Q. And there -- but there are examples of HCl salts, right?
A. Yes. That's right, that's a common salt.
Q. And if we go back to that definition of the pharmaceutically acceptable acid addition salts --
MR. PRUSSIA: We can leave that on the screen.
BY MR. PRUSSIA:
Q. -- HCl is a pharmaceutically acceptable acid addition salt according to the '473 patent; right?
MR. PRUSSIA: You can highlight it, Tom, hydrochloric acid.
THE WITNESS: Yes, I see hydrochloric acid there.
BY MR. PRUSSIA:
Q. And nothing in the '473 patent discloses any issues with the HCL salts that were exemplified in the patent; correct?

A. In the case of cabozantinib, you mean, or any of them?

Q. Anywhere in the patent?

A. Not as far as I'm aware.

Q. And the patent also discloses an example of a compound that was made with dihydrobromide salt; correct?

A. Do you want to direct me to that?

Q. Sure.

MR. PRUSSIA: If we go to Example 15 at Column 295 of the patent.

Actually, why don't we pull up your -- I can refresh your recollection through your deposition testimony. If it's -- it's in your binder, Volume I, Tab 6. We'll put it on the screen. At Line 230 -- Page 232, Line 12 to 16.

And the question was:

"QUESTION: And Example 15 describes a formation of a dihydrobromide salt; correct?"

And your answer was, "Yes, the product seems to be a dihydrobromide. Yes."

THE WITNESS: Okay.

BY MR. PRUSSIA:

Q. Does that refresh your recollection?

A. It does, yes. I obviously said that.

Q. And so my question is, correct, that there is an example of a dihydrobromide salt in the '473 patent

specification; correct?
A. Yes, seems to be.
Q. And dihydrobromic acid is a pharmaceutically acceptable acid addition, according to that patent; correct?
A. I'm sorry, are you saying dihydrobromic acid?
Q. Hydrobromic acid.
A. Hydrobromic. Well, the patent -- how does it define it?
It gives that as an example of an acid, I don't believe it's GRAS, but yeah.
Q. Okay. Just to sum up, the '473 patent specification provides specific examples of salts using at least some of the 24 listed pharmaceutically acceptable acid additions.
We agree on that; right?
A. Correct.
Q. And we agree that none of those salts were malate salts; right?
A. Correct.
Q. And none of those salts involved cabozantinib; correct?
A. Correct.
Q. And the '473 patent does not disclose a need to form a salt with the free base form of cabozantinib; right?
A. Not as far as I can recall.
Q. Now, I know you started to talk about and the like,

11:34:31 so we'll come back to it.

11:34:33 In rendering your opinions in this case, you did not identify what acids would be like, the 24 acids listed in the '473 patent; right?

11:34:41 A. No. I mean, those would be prior art kind of acids in the way that I've described.

11:34:47 Q. You do not discuss this language in your reports in this case; correct?

11:34:50 A. Not as far as I can recall.

11:34:52 Q. And in connection with forming your opinions in this case, you did not consider the pK_a values for any of the 24 listed acids when forming your opinions; right?

11:35:02 A. I think many of those are on the prior art list and so I would have considered their pK_a values.

11:35:09 MR. PRUSSIA: We can go to your deposition. Page 247, Lines 10 to 13.

11:35:14 Sorry, it's the Tab 7. It's Tab 7 in your binder, Volume I. Yeah.

11:35:37 The question was: "It's not something you've considered in connection with forming your opinions in this case?"

11:35:48 And the answer was: "I didn't look at the pK_a values of this particular list of acids."

11:35:51 BY MR. PRUSSIA:

11:35:53 Q. Is that the question and that was your answer?

A. Yes. What I meant by that is I didn't look at them as a list as a whole. Obviously, some of the acids on there are on the documents that I presented.
Q. Now, as of the priority date, there were at least 113 pharmaceutical salts that had been approved -- had been used in approved drug products; correct?
A. Yes, that sounds about right.
Q. You did not evaluate which of the 113 counterions used to make those salts were like the 24 listed in the '473 patent; right?
A. I suppose I didn't consider it that way; that's correct.
Q. And in this case, you do not offer -- strike that.
On your direct, you did not offer the opinion that a person of skill would have at once envisaged the crystalline malate salt from the genus of pharmaceutically acceptable salts of cabozantinib; right?
A. No, I'm not offering that opinion.
Q. Now, a skilled artisan would only consider making a salt if there were problems with the free base; right?
A. They would consider it as part of optimization of the properties of the active pharmaceutical ingredient.
Q. My question was correct; right?
A. Yes. I suppose if there were no problems with the free base, then -- then they might pursue the free base as a

first formulation option, that's right.

Q. Because there would be no reason to pursue a salt; correct?

A. Yes. If -- I suppose if there was a solubility issue of the free base, as is the case here, then that would be a reason to pursue a salt.

Q. And there were no specific disclosures in the prior art that the cabozantinib free base had any problems with its oral bioavailability; correct?

A. No disclosures, but that's part of the solubility measurements that I mentioned.

Q. My question was correct; right?

A. That's right.

Q. For example, the '473 patent does not disclose that cabozantinib was poorly absorbed in the gastrointestinal tract; correct?

A. Not as far as I can recall.

Q. And, in fact, there was no oral bioavailability data for the cabozantinib free base reported in the prior art; correct?

A. Not as far as I'm aware.

Q. So as of the priority date, a skilled artisan would not have known what the oral bioavailability of cabozantinib was; right?

A. That's correct.

Q. And you are not aware of whether the acceptable -- strike that.

And identifying an acceptable bioavailability is not something that you are qualified to do; isn't that right, sir?

A. Yes. I typically don't run pK_a studies. But obviously you want a high bioavailability, otherwise it wouldn't work.

Q. Now, you agree that there's more to oral bioavailability than solubility; correct?

A. That's correct, yes. Permeability is also important.

Q. It's certainly relevant. Permeability is certainly relevant to bioavailability; correct?

A. Correct.

Q. And you did not explicitly consider the permeability of the cabozantinib free base in connection with forming your opinions; right?

A. That would typically come after the sort of salt screening that I described.

Q. So my question was correct; right?

A. That's right.

Q. And so you did not consider whether the cabozantinib free base had high permeability in connection with forming your opinions; right?

A. Not directly, no. Obviously low solubility would

still give rise to low bioavailability, even with high permeability.
Q. And there are drugs that have low solubility that have sufficient bioavailability as a result of their high permeability; correct?
A. I'm not aware of the specific example you're talking to. It depends how -- low is low, of course.
Q. Well in connection with forming your opinions regarding motivation, it was beyond your expertise to consider whether cabozantinib was such a drug; right?
A. Yes, that's right.
Q. Now, as of the priority date, solubility data for cabozantinib had not been identified in any prior art reference; correct?
A. That's true, but it would be easy to measure.
Q. And as of the priority date, there was no prior art reference describing the cabozantinib free base as insoluble; correct?
A. No. But, again, easy to measure.
Q. And as of the priority date, there was no data whatsoever identifying cabozantinib solubility in biorelevant media; correct?
A. Again, no. But it would be easy to measure.
Q. And is it your opinion that a person of skill would do that?

A. Under what circumstances?

Q. Well, under the circumstances that you considered in this case.

A. Measure solubility in biorelevant media, you mean?

Q. Yes, sir?

A. Not as an initial part of the salt screen, no.

Q. Okay. Now, the prior art did not disclose the target solubility for cabozantinib; correct?

A. That's correct.

Q. Now, it's your opinion, as you just testified, that a person of skill could have identified the solubility of the cabozantinib free base through experimental testing; right?

A. Correct.

Q. And I believe on direct you testified, and I wrote it down, "typically you wouldn't want to use an amorphous salt, unless there was a particular reason to do so such as a need to improve solubility"; correct?

A. Correct.

Q. And we agree that there was no data in the prior art regarding the solubility of cabozantinib; right?

A. That's right.

Q. Now, with respect to testing, there are many properties of a drug that a skilled artisan will take into consideration early in the drug development process; right?

A. Yes. I suppose that's true.

Q. And you say that a person of skill could have tested the water solubility of cabozantinib; right?
A. That's right.
Q. That same person of skill could have determined the bioavailability of the cabozantinib free base through testing; right?
A. Yes, that's right. That would be like an in vivo kind of test.
Q. And that would be a routine experiment in your view; right?
A. Yes, I suppose it would.
Q. And a skilled artisan could have developed determine the permeability of the cabozantinib free base through testing; correct?
A. Correct.
Q. But in rendering your opinions, you have not explained why a skilled artisan would only measure the water solubility of the cabozantinib free base without additionally measuring the permeability or bioavailability; right?
A. So the experiments you're talking about would come after the salt screen.
Q. Now, the (L)-malic acid salt is complicated because the anion can exist as both single and doubly deprotonated species; right?

A. This particular malic acid salt is not complicated because the second pK_a is not acidic enough to protonate cabozantinib.

Q. All right. Let's go to your deposition.

MR. PRUSSIA: It's Tab 7, page 304, 14 to 24.

The question is: "If we turn to Page 1064 of the black paper, under the discussion section, and the second paragraph under that section on the left-hand column, about halfway down, there is a sentence that reads, 'The fate of the (L)-malate salt is more complicated because the anion can exist as both single and doubly deprotonated species.

"Do you see that?

"ANSWER: I do.

"QUESTION: And that is a correct statement?

"ANSWER: That's right."

BY MR. PRUSSIA:

Q. Those were my questions and those were your answers; correct?

A. That's right. But that's not specifically cabozantinib (L)-malate. It's (L)-malate in general.

Q. My question was: The (L)-malic acid is complicated because as anion can exist as both singly and doubly deprotonated species; correct?

A. Yes. It does have two pK_a values, that's right.

Q. That would have made the (L)-malate salt acid -- strike that.
That would have made the malic acid a more complicated choice; correct?
A. It's not something that wouldn't be controllable. It's just another consideration that would go into the process.
Q. Now, as of the priority date, the hydrochloride salt was by far the most common salt; right?
A. Correct.
Q. And, in fact, in your tutorial to the Court you showed an example of forming a salt with chlorides; right?
A. Yes. That's right.
Q. And that's because it's -- in your opinion, it's the first salt that a person of skill would consider; right?
A. Yes, that's right.
Q. And the reason for that is because it's a strong acid that tends to protonate those things; right?
A. Yes, that's one reason.
MR. PRUSSIA: And if we go to PTX-331. It's at Tab 14 of your binder. We'll pull it up.
BY MR. PRUSSIA:
Q. This is the -- I like to call it Bighley. I know you said Bighley, you're British so you are probably right.
The Bighley reference, we'll put that up on the

screen.

A. Never heard it said, so who knows.

MR. PRUSSIA: And if you look at Page 484, about halfway down, under the heading "Preparation of the hydrochloride salt."

BY MR. PRUSSIA:

Q. Bighley discloses that "Hydrochloride is by far the most popular salt form of basic compounds"; correct?

A. Yes.

Q. And you agree with that; right?

A. Yeah, I do.

MR. PRUSSIA: And if we go Table 1.

BY MR. PRUSSIA:

Q. The percent column gives the relative frequency of use for each salt type based on the total number of salts used through 1993; correct?

A. Yes. That's right.

Q. And if we look at the reference for hydrochloride, we see that it had been used almost 44 percent of the time as of that date; right?

A. Yeah, very common.

MR. PRUSSIA: And if we look at the entry for malic acid on the next page.

BY MR. PRUSSIA:

Q. The frequency of use of that was only 0.26 percent;

right?

A. Yeah, correct.

MR. PRUSSIA: Now, if we turn to PTX-549.

BY MR. PRUSSIA:

Q. This is the Paulekuhn reference that you testified about during your direct; right?

A. Correct.

Q. And the article is titled, "Trends in Active Pharmaceutical Ingredient Salt Selection Based on Analysis of the Orange Book Database"; correct?

A. Correct.

Q. And so this article addresses trends in the API salt selection process; correct?

A. Yes.

Q. And the authors here were affiliated with Merck; right?

A. Yes. That's right.

Q. And if we look under the study design, the authors compiled data from the FDA Orange Book Database as of the end of 2006; right?

A. Yes, that's my understanding.

MR. PRUSSIA: And if we turn to the second sentence in that paragraph.

BY MR. PRUSSIA:

Q. The authors identified 1,356 chemically well-defined

APIs; correct?
A. Yes.
MR. PRUSSIA: And if we turn to the results and discussion section, under the next page.
BY MR. PRUSSIA:
Q. The authors identify that 659 of those APIs were in non-salt forms; correct?
A. Correct.
Q. So for nearly half of all APIs listed in the Orange Book, the authors identified them as being in non-salt forms; correct?
A. Yes, that's right.
Q. 523 salts were formed from basic compounds; correct?
A. Correct.
Q. And that's about 38.6 percent of all APIs listed in the Orange Book; right?
A. Yes.
Q. And cabozantinib appears, it would be a basic compound; correct?
A. That's right.
MR. PRUSSIA: And if we turn to Table 2 at Page 3.
BY MR. PRUSSIA:
Q. The results of the study showed that as of 2006, over 50 percent of all salts were chloride salts; right?

A. That's right.
Q. By comparison, the malate salt was used in just 0.4 percent of all products across the Orange Book as of 2006; right?
A. I'm sure you're right. I'm just looking for it.
MR. PRUSSIA: Can we highlight it in -- there we go.
THE WITNESS: Yeah, that's correct.
BY MR. PRUSSIA:
Q. And that's about two salts total; right?
A. I trust your math. So, yes, that's about right.
Q. Okay. And then we can see that one was approved in -- well, strike that. We can see that one was approved pre-19 -- in the pre-1982 time frame; right?
A. Right.
Q. And the other was approved in the 2002 to 2006 time frame; correct?
A. Right.
Q. And in between them you have a gap between 1982 and 2002 where there wasn't a single FDA-approved drug that was a malate salt; right?
A. Correct.
Q. And if we turn back to the study design on the first page, the authors identify Category I APIs.
Do you see that?

A. Right.
Q. And Category I APIs were salt -- were identified as salts formed from basic molecules containing at least one atom suitable for protonation; correct?
A. Correct.
Q. And this cabozantinib would fall under Category I; correct?
A. Yes, I believe so.
Q. And if we go to Figure 2, Paulekuhn includes a pie chart depicting the overall distribution of anions of Category I in the Orange Book; right?
A. Yes.
MR. PRUSSIA: And if we could pull up the PDX.
BY MR. PRUSSIA:
Q. We can see that what I've done is I've taken the chloride salts as depicted in the top half of the figure and I've shaded it in green.
Do you see that?
A. I do.
Q. That's a pretty big piece of the pie; right?
A. Yeah, big percentage.
Q. Now, we have malate listed there as well; right?
A. Correct.
Q. Highlighted that in blue. May be tough to see the type. It's a tiny sliver; right?

11:49:55 A. Yes, I can see it, but I agree.
11:49:57 Q. Now, you've offered the opinion that a skilled artisan would have a relatively short list of anions that would have been obvious to try: Citrate, fumarate, gluconate, lactate, malate, maleate, succinate and tartrate; right?
11:50:13 A. Yes, that's based on the reference I was alluding to.
11:50:17 Q. And that was from your report in this case; right?
11:50:19 A. I believe so. Yes.
11:50:20 Q. So let's put that list on this, on the PDX, and let's compare your list of anions with the overall distribution of anions as disclosed in Paulekuhn; okay?
11:50:33 So what I've done is we've shaded your anions in purple along with malic acid in blue; okay?
11:50:40 Do you see that?
11:50:41 A. I do.
11:50:41 Q. And that represents your narrowed list of anions that you say a person of skill in the art would have focused on; right?
11:50:49 A. Right.
11:50:50 Q. And if we go to the next slide, we have the definition of pharmaceutically acceptable acid addition salts in the '473 patent.
11:51:01 Do you see that?
11:51:01 A. I do.

Q. And I've highlighted the ones from your list that also appear in that list. Okay?
A. Okay.
Q. Now, let's see what's missing from your list. Missing from your list -- we highlighted in green -- is the hydrochloric acid; right?
A. Okay.
Q. So you've excluded that from your list; correct?
A. Yes, I think -- I think I explained the origins of my list in the previous -- previous sections.
Q. Well, sir, but my question is correct. You've excluded it from your list; right?
A. By the time you get to this point of the report, that's true, yes.
Q. And the largest slice of the pie you've excluded from your list; correct?
A. Not in terms of what would be included in a salt screen. But the fact that malate would be an obvious one to include in the salt screen.
Q. You've excluded bromide; right?
I shaded that in green.
You've excluded mesylate; correct?
Shade that in green.
You've also excluded sulfuric acid; correct?
A. No. I don't think I especially excluded inorganic

acid from the salt screen.

Q. I'm just looking at your list that we just agreed on was your final list. It's not -- sulfuric acid is not on that list; correct, sir?

A. I have to look at the context of that -- that paragraph.

Q. This is from your own report.

A. Yeah.

Q. This is the list that we just a few minutes ago agreed on was your final list?

A. There's a preamble discussion of that that I need to know the context of -- of that.

Q. Okay. Your counsel can ask you on redirect, so -- but sulfuric acid is not on that list; correct?

A. Not in the Paragraph 399 list.

Q. And if we populate all of the acid that is not on that list, what we have on the slide -- you can go ahead and fill them all in -- we have a depiction of every acid that you've excluded from your list shaded in green or light green as compared to the ones that you've included in purple; correct?

A. Yes, I think the list at Paragraph 399 wasn't intended to include the inorganic acids. It's just the organic acid list.

Q. Now, in your opinion, the Tong and Whitesell

Rule-of-2 --

MR. PRUSSIA: We can take that down.

BY MR. PRUSSIA:

Q. -- is a good starting point for salt screening; correct?

A. Yes, that is certainly one important consideration.

Q. And in this case, you use the Rule-of-2 to identify acids for a cabozantinib salt screen; right?

A. Yes, this is one of the considerations.

Q. And you use it to eliminate potential counterions from a cabozantinib salt screen because they don't meet the Rule-of-2; right?

A. Yes. They wouldn't be acidic enough.

Q. But in addition to a Rule-of-2, the prior art describes a Rule-of-3; correct?

A. Yes, we discussed this at the deposition.

Q. And during your direct you didn't offer any opinions regarding the Rule-of-3; right?

A. There's a sliding scale of acidity which starts at 2 pH units and becomes increasingly likely to form a salt as you get towards 3, 4 and so on pH units likely.

Q. Sure. My question was correct. You didn't explain anything to Judge Andrews about the Rule-of-3 during your direct; right?

A. From a pH difference of 2 onwards, it becomes

increasingly likely that a salt will form.

Q. Now, the Rule-of-3 holds that for the formation of a stable salt, there should be a minimum difference of three units between the pK_a of the free base drug and the acid; correct?

A. I think you're quoting from a reference that says "around 3" if I remember rightly.

MR. PRUSSIA: Let's pull up your deposition. It's Tab 6, Page 298, 9 through 15.

The question was: "Okay."

Now about halfway down, it says, "As read, it is generally accepted that there should be a minimum difference of 3 units between the pK_a value of an ionizable group and of the possible counterion.

"Citing Bowker in 2002; correct?

"ANSWER: That's what it says."

THE WITNESS: I seem to recall that there was an approximately in there.

BY MR. PRUSSIA:

Q. That was my question and that was your answer; correct, sir?

A. I think it's out of context.

Q. Well, you do not apply the Rule-of-3 in connection with forming your opinion in this case; right?

A. As I explained to you at length in the deposition,

from pH difference of two units onwards, the increase in -- the formation of a salt becomes increasingly likely.

Q. Well, let's see what you said in the deposition.

MR. PRUSSIA: Let's go to Page 303, Lines 14 to 17.

"You only make reference to a Rule-of-2 in your reports; right?

"ANSWER: That's right because that's where you start -- that's where you start to get salts forming."

That was my question and that was your answer; correct?

THE WITNESS: That's right.

BY MR. PRUSSIA:

Q. Now, the pK_a of cabozantinib, it was not known as of the priority date; right?

A. No, but as I said, easily measured.

Q. And you offer the opinion that it would be expected to be a 5.8 to 5.9; right?

A. Yes, I believe that's my recollection.

Q. And you don't cite any documents to support that opinion; right?

A. As you said, it wasn't known. It would be easily measured.

Q. Okay. Now, let's work with your pK_a number of cabozantinib as a pK_a of 5.8 to 5.9, and let's write it on

the board. Can I write down -- which one do you want me to write down, 5.8 or 5.9?

A. 5.9, I guess.

Q. What's the pK_a of malic acid?

A. It's 3.4, I think.

Q. What's the answer to 5.9 minus 3.4?

A. Two and a half.

Q. So the -- so the pK_a of malic acid would not be within three units away from cabozantinib's pK_a; correct?

A. That's right. Two and a half.

Q. So malic acid would not meet the Rule-of-3 as applied to a cabozantinib salt screen; correct?

A. As I explained to you, as the pH difference increases the likelihood of salt formation increases, and there's a well-defined study showing that from two onwards the likelihood of salts number very high.

Q. Had you applied the Rule-of-3 as you did the Rule-of-2 in your opinions, you would not have identified malic acid as a counterion for cabozantinib; correct?

A. Well, it's not really the Rule-of-3. It's the Rule-of-2 and above in my opinion. If you slavishly adopted the three point without looking beyond it, then the difference wouldn't be three, but that's not a way a person of skill would proceed.

Q. Now, during direct, you showed the Court Table 2 from

the Stahl reference; right?

A. Correct.

MR. PRUSSIA: Let's put that on the screen.

BY MR. PRUSSIA:

Q. And you drew a red line for where the line -- for where the Rule-of-2 cut off the list; correct?

A. Correct.

Q. And you pointed Your Honor to above the line so that you could point to malic acid; right?

A. I pointed to all the acids that were above the line.

Q. Right. Now, let's see what happens when you draw the red line applying the Rule-of-3.

Malic acid is not above the line; correct?

A. That's correct. But that's not the way a person would proceed.

Q. Now, the Rule-of-3 was widely accepted by skilled artisans as of the priority dates; correct?

A. I think skilled artisans had a much broader understanding than just going with numbers 2 or 3, 2 and above.

Q. The Rule-of-3 was reported in the literature as of the priority date; correct?

A. There was discussion in the literature about the kinds of pK_a difference that were needed.

Q. And the literature reported that the Rule-of-3

especially applied when the drug substance is a particularly weak base; right?
A. Some people said that kind of thing. But that's -- that's an out-of-context discussion.
Q. Actually, I just want to make one thing clear. Do you or do you not agree that the Rule-of-3 was widely accepted by persons of skill as of the priority date?
A. I don't know that I could say widely or not. I've read the details of this and there's a well-informed study that shows how salt formation increases as the pK_a difference increases, as I explained to you at the deposition.
Q. Okay.

MR. PRUSSIA: Let's mark -- let's go to PTX-322.

BY MR. PRUSSIA:
Q. This is a paper titled "Salt Selection and Optimisation Procedures For Pharmaceutical New Chemical Entities."

Do you see that?
A. I do.
Q. And it was published in 2000; correct?
A. Yes.
Q. And the last name of the first listed author is Bastin; correct?
A. Correct.

Q. And this Bastin publication was available to skilled artisans as of the priority date; right?
A. Yes.
Q. And I believe a minute ago you couldn't agree with my question as to whether the Rule-of-3 was widely accepted in the literature; correct?
A. Yes, I don't personally have an opinion whether it's wide or not.
Q. Okay. So if we go to the bottom of the paragraph in the right-hand of the column of the first page, we can see the sentence starting "for formation of a stable salt."
Do you see that?
A. Yes.
Q. You can see that Bastin discloses that it is widely accepted that there should be a minimum difference of about three units; correct?
A. Yes, about three units.
Q. Right. Widely accepted; correct?
A. That's what this particular paper is suggesting.
Q. By everyone except you; right?
A. No, not by everyone except me.
Q. Because if you had applied the Rule-of-3, malic acid would have been excluded; right?
A. Like I said, it's not a hard-and-fast rule. It's a tendency increasing from pK_a and its two onwards.

Q. Now, Bastin goes on to disclose that this is especially true when the drug substance is a particularly weak acid or base; correct?
A. Yes. If it was a strong acid or base then they wouldn't really be talking about the importance of small differences of pK_a units.
Q. Now, you don't offer any opinion in your reports explaining why a person of skill in the art would have ruled -- ignored the Rule-of-3, like you did, in favor of the Rule-of-2; correct?
A. I can't recall exactly what I say in my report. But as I said to you at deposition quite extensively, there's an increasing tendency from two pK_a units onwards for salts to form.
Q. Now, during your direct, you talked a little bit about Sutent, sunitinib.
Do you remember that?
A. Yes, I mentioned that.
Q. And you offered the opinion that a skilled person would have been motivated to select malate because it had been used as a salt form for Sutent; right?
A. I mentioned that that was also around the literature, although I did point out that it's a different compound, of course.
Q. Now, when you say "it was in the literature," just to

be clear, you didn't identify it; correct?
A. No, it wasn't me that found that article, that's correct.
Q. The Sutent label was given to you by MSN's lawyers; right?
A. That's correct.
Q. So it's not something that you, as a skilled person, came across in the regular course; right?
A. It would have been available to a skilled person, but yeah, I personally didn't find it.
Q. And you didn't research other FDA-approved kinase inhibitors or identify their salt forms; right?
A. No, I didn't undertake a literature study of that kind.
Q. You only picked out Sutent; correct?
A. As an example.
Q. Let's talk a little bit about reasonable expectations, all right?
Now, the malate salt of cabozantinib, it's not the most soluble salt; right?
A. It's among the most soluble salts that have a nice favorable balance of pharmaceutical properties.
Q. It's not the most soluble salt, sir, is it?
A. Numerically, no, I think there's a couple of alkane sulfonate salts that are somewhat more soluble but have

issues.

Q. So if a person of skill in the art -- strike that.

MR. PRUSSIA: Let's pull up PTX-265.

BY MR. PRUSSIA:

Q. Now, this is an Exelixis patent publication ending in 166. And you've seen this patent before; right?

A. Was this the one you showed me at deposition?

Q. That's right, sir.

A. Yeah, I think I saw it there for the first time.

MR. PRUSSIA: Now, if we turn to paragraph 3 on Page 69.

BY MR. PRUSSIA:

Q. The structure of cabozantinib is shown here, and it's defined as Compound I, do you see that, sir?

A. Yeah.

Q. And the 166 publication describes salts of cabozantinib; right?

A. I believe so.

MR. COOPER: Objection; Your Honor, this is not prior art.

MR. PRUSSIA: It's cross-examination.

THE COURT: Well, I'm going to overrule the objection.

MR. PRUSSIA: Turn to paragraph 501, please.

BY MR. PRUSSIA:

Q. Now, the patent discloses the pyruvate salt of cabozantinib; right?
A. Yes, I believe so.
Q. And the patent discloses that the pyruvate salt has an aqueous solubility of 0.33 mgs per ml. Do you see that?
A. Yes.
Q. And that's more soluble than the malate salt of cabozantinib; right?
A. It is. It makes mention of a particular pH, so I don't know what cabozantinib's solubility at that pH is.
Q. Now, pyruvic acid has a pK_a of 2.39, you know that; right?
A. I hadn't remembered it offhand but I'll take your word for it.
Q. Do you want to be refreshed on that?
A. I'll take your word for it.
Q. Okay.
A. It sounds right.
Q. So pyruvic acid would have satisfied the Rule-of-2 for cabozantinib --
THE REPORTER: I'm sorry. Can you repeat the question?
THE WITNESS: You said 2.89; right?
MR. PRUSSIA: I'm just -- we need to -- for the reporter.

BY MR. PRUSSIA:
Q. So pyruvic acid would have satisfied the Rule-of-2 for cabozantinib; correct?
A. You said 2.89; right?
Q. 2.39.
A. 2.39, yes, it would.
Q. So if a skilled person had included pyruvic acid in a salt screen for cabozantinib, that skilled person would have learned that the pyruvate salt has better water solubility than the malate salt; right?
A. Yes, I suppose that's true. I can't speak to its other properties.
Q. But you don't offer any explanation for why a person of skill would have picked the malate salt over the pyruvic salt; correct?
A. That's true.
Q. Now, a skilled person would not have known whether a counterion would form a salt with cabozantinib until they tried it; correct?
A. Yes, that's what the screen process is. Although -- yeah, just repeat the question.
Q. Sure. A skilled person would not have known whether a counterion would form a salt with cabozantinib until they tried it; correct?
A. Wouldn't have known whether it was an isolated or

solid crystalline salt that's nonhygroscopic and so on in solution. The pK_a would tell you.

Q. No, that's not my question, sir.

A skilled person would not know whether a counterion would form a salt with cabozantinib until they tried it; correct?

A. In solution, they would know because of the pK_a difference. As a crystalline or isolated solid, they wouldn't know, they would try it.

Q. Okay. Now, salt selection is an empirical process; right?

A. Yes, that's right.

Q. You actually need to form each salt and study it in order to determine which one is the right one; right?

A. Yes, that's correct.

Q. And the typical way the field proceeds is to make the salts and then study their properties; correct?

A. That's correct.

MR. PRUSSIA: If you pull up PTX-333.

BY MR. PRUSSIA:

Q. This is a paper by Simon Black; correct?

A. Correct.

Q. It's title "Structure, Solubility, Screening, and Synthesis of Molecular Salts"; correct?

A. Correct.

Q. And it was published in 2007; correct? 2006, sorry.
A. Yes.
Q. And if we take a look at the abstract, and focus on the third sentence that starts "this means that as of" -- as of the priority date, Black disclosed that "the ability to predict which salt forms will have desirable physical properties is essentially non-existent"; correct?
A. Yes, that's what it says, yeah. And that's why we do screen.

MR. PRUSSIA: If we pull up PTX-327.

BY MR. PRUSSIA:
Q. This is the Berge reference that you testified about on your direct; correct?
A. Correct.
Q. And it's published in 1977; correct?
A. That's right.
Q. So it was available to a skilled person; right?
A. Correct.
Q. And if we turn to the paragraph under table of contents, and there's a line starting with "choosing the appropriate salt."

Are you with me?
A. Yes.
Q. As of the priority date, Berge disclosed that "choosing the appropriate salt can be a very difficult

task." Correct?
A. Yes. And I think he's referring to choosing the appropriate salt for the final formulation, because he's talking of properties here, not choosing what to include in the salt screen.
Q. And Berge disclosed that this is because each salt imparts unique properties to the parent compound; correct?
A. Correct, yes.
Q. And turning to the top of the next paragraph, Berge disclosed that "salt-forming agents are often chosen empirically." Correct?
A. Correct.
Q. And you agree with that; right?
A. Well, empirically, I suppose, refers to the actual making that you were describing. So, I think what he's saying here is that you run the salt screen and then you choose which one that you're going to pursue based upon that empirical salt screen.
Q. And Berge goes on to disclose, "Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound"; correct?
A. Yes. That's right. That's why you do the empirical salt screen to see experimentally what the behavior would be, although you'd have an expectation that typically salts

are more soluble.
Q. Now, not all salts are crystalline; correct?
A. Correct. Although, the majority are.
MR. PRUSSIA: Pull it down.
BY MR. PRUSSIA:
Q. A salt can either be crystalline or amorphous; right?
A. Correct.
Q. And the Rule-of-2 does not guarantee that a crystalline material will be formed; right?
A. That's right.
Q. You actually have to make the material and see what properties it has; right?
A. Yes. Very often it will crystallize, but it's not guaranteed, might be hygroscopic, for example.
Q. And, in fact, you made reference on your direct to the Tong reference.
Do you remember that?
A. Correct.
Q. And, in fact, in that paper itself there's an example where one-third of the salts that were formed did not result in crystalline material; correct?
A. I think the Tong reference is a method development paper that only looks at six, and by one-third you mean two of them weren't crystalline?
Q. Yes, sir. My question was correct?

A. So, yes. They weren't obviously trying to crystallize them. They were trying to develop a method to -- to fast track the solubility measurements.
Q. I understand all that, sir.
My question was correct; right?
A. So I think two of the six they studied didn't crystallize in their study, if I recall correctly.
Q. Now, when conducting a salt screen, you wouldn't have an expectation as to whether a particular counterion would be the right choice for a particular drug substance; right?
A. That's right. You wouldn't know the outcome of the salt screen before you did it.
Q. You have to do the salt screen; right?
A. Correct.
Q. And then have you to characterize the products of that salt screen; right?
A. Yes, that's right.
Q. And a person of skill would not have had an expectation in advance of what particular acid would provide the right properties for the drug substance when it's formed as a salt; right?
A. That's right, yes. That's why they would do the screen.
Q. And the selection of the ultimate salt is determined on a case-by-case basis; right?

A. Yes. Based on the properties of the -- of the materials that are isolated in the salt screen.

Q. Now, shifting gears a little bit. You agree that a person of skill would expect that low water solubility will correlate with a slow dissolution rate; right?

A. Typically that's right, yes.

Q. And you agree with the general statement that a amorphous solids typically undergo dissolution at a faster rate, as compared to crystalline solids; right?

A. Yes. They do, unless there's a particular issue with clumping or something like that, as there is here.

Q. Now, you also offer opinions in this case regarding Section 112; right?

A. Correct.

Q. And you offered some opinions this morning to Your Honor with respect to the meaning of the word "crystalline"; right?

A. Yes.

MR. PRUSSIA: Now let's take a look the '439 patent, Claim 1.

BY MR. PRUSSIA:

Q. And just focusing on the claim, we can agree that there are just three elements of the claim; right?

A. I suppose so, yes.

Q. The first element is that the material is

cabozantinib; right?
A. Correct.
Q. The second element is that the material is a malate salt of cabozantinib; correct?
A. Correct.
Q. And the third element is that the material is crystalline; right?
A. That's right.
Q. And in the context of this claim, the word crystalline is being used as an adjective to describe the solid matter of cabozantinib; right?
A. Yes. It has to be -- has to be crystalline in the sense that it has to have that regular underlying arrangement of the molecules.
Q. And this is generally true throughout all of the claims; right? All in which crystalline is being used.
A. Yes, I think it's consistent.
Q. Yeah. And crystalline refers to a crystal in which the structural units are repeated regularly in three dimensions; correct?
A. Yes, that's right. That's a good, broad definition of crystalline.
Q. And that definition reflects the plain and ordinary meaning of the term crystalline as of the priority date; correct?

A. Yes, I suppose so. I mean there some nuances to it, but yes. It would have that regular, repeating periodic arrangement as I described.
Q. Right. So just to be clear, the plain and ordinary meaning, you would agree, is a crystal in which the structural units are repeated regularly in three dimensions; correct?
A. Yes. That would be one good definition of crystallinity. As I say, there may be some nuances to it. Those are layman's definitions.
Q. And if the material has no repeating internal structure, then it's amorphous; right?
A. Yes. I suppose that's true as well.
Q. So that means that a solid that is not amorphous is not -- strike that.
That means that a solid that is amorphous is not crystalline; correct?
A. Yes, that's right. Amorphous solid is not crystalline.
Q. And that's how the patent defines it too; correct?
A. How it defines amorphous, you mean?
Q. Right.
A. I don't recall offhand, but we can look at that.
Q. Maybe we'll come back to it.
But just focusing on the claims, the word

"forms," it doesn't appear anywhere in this -- in the asserted claims; right?

A. The word is not there, but of course it's implicit. You can't be crystalline without be being in a particular crystalline form.

Q. Well, the literal word does not appear in the claim. So you can agree on that basic concept; right?

A. You're right. The word isn't there in the language.

Q. And you agree that the claims do not require all crystalline forms; right?

A. The claims encompass anything that is an (L)-malate salt, which is crystalline.

Q. Well, the claim doesn't require all crystalline forms, that's your opinion; right?

A. In -- you mean in order to satisfy the written description requirement?

Q. Well, let's refresh you.

MR. PRUSSIA: Let's go to deposition, Page 97, Lines 17 to 24.

The question is: "Under this scenario where the claim is not interpreted to require all crystalline forms, you don't have an opinion with respect to 112; right?

"The claim doesn't require all crystalline forms. It requires the cabozantinib malate to be crystalline, that's the way the claim is written and the way

a person of skill would understand it."

BY MR. PRUSSIA:

Q. That was my question, that was your answer; correct?

MR. COOPER: Objection. Improper impeachment, Your Honor.

THE COURT: All right. Overruled.

BY MR. PRUSSIA:

Q. So the claims -- you agree that claims do not require all crystalline forms; right?

A. Yes.

Q. The claims simply require cabozantinib malate to be crystalline; correct?

A. Yes. And I've explained that needs to be in a particular crystalline form and the claim does encompass anything that is in a crystalline form that's cabozantinib malate.

Q. Well, the way the claim is written is simply to require the cabozantinib malate to be crystalline; correct?

A. Yes, that's correct.

Q. And that's the way a person of skill would understand it; correct?

A. A person of skill would know what crystalline meant and know that there had to be a regular repeating underlying arrangement of molecules to be crystalline, and I think they would interpret it that way.

Q. Now, you reviewed the prosecution history for the crystalline malate salt patents; correct?
A. Yes. It's been a while, but yes.
Q. And the patent examiner did not issue any rejections under 112 during prosecution; correct?
A. Not to my recollection, no.
Q. The patent examiner never issued a rejection saying, hey, these claims require a genus of forms, you don't describe that; correct?
A. That's correct.
Q. Now, this -- let's talk about what is disclosed in the specification.
Cabozantinib is disclosed; correct?
A. I believe so.
Q. The (L)-malate salt of cabozantinib is disclosed; correct?
A. Correct.
Q. The (D)-malate salt of cabozantinib is disclosed; correct?
A. Can you direct me to that?
Q. Sure.
MR. PRUSSIA: Let's go to JTX-1, Column 6, Line 56 to 64. And I believe you also showed this on your direct.
Keep it up and I'll just re-ask the question.

BY MR. PRUSSIA:
Q. The specification discloses the (D)-malate salt of cabozantinib; correct?
A. Yes. It describes it in the disclosure. I don't think there are any actual examples of them actually making a (D)-malic acid salt, if I remember rightly.
Q. The specification discloses the (D)-malate salt of cabozantinib; correct?
A. Yes, I see it written there.
Q. Okay. The specification discloses how to make cabozantinib (L)-malate; correct?
A. Yes, I believe it does.
Q. And the prep -- in the preparative examples in the specification, right?
A. Correct.
Q. And those preparative examples disclose how to make crystalline cabozantinib (L)-malate; correct?
A. In forms N-1 and N-2, yes.
Q. My question is correct, the preparative examples disclose how to make crystalline cabozantinib (L)-malate; right?
A. Yes.
Q. Now, the specification discloses the chemical formula for crystalline cabozantinib (L)-malate; correct?
A. I believe it does, yes.

Q. And you agree that all crystalline cabozantinib (L)-malate will have the same chemical formula; right?
A. They will unless they're solvates, in which case there will be solvent molecules there as well.
Q. And all crystalline cabozantinib (L)-malate will have the same chemical makeup; correct?
A. They will unless they're solvates in crystalline forms, in which case there will be the solvent there as well.
Q. Now, let's talk a little bit about your opinions regarding polymorphs.
You agree that the pharmaceutically relevant polymorphs are those crystalline forms that are likely to arise during the normal course of drug development; right?
A. Yes. I guess that's true.
Q. And typically the most pharmaceutically relevant forms are those that are the most stable; right?
A. Yes, let me suppose it's an important consideration.
Q. And the N-1 form is the most thermodynamically stable form of cabozantinib malate; right?
A. It is of the ones that we know of so far, as far as I understand it.
Q. And you generally agree that it is important to identify stable polymorphic forms for pharmaceutical development; right?

A. Yes, absolutely.
Q. And the first form that a person of skill would look at is the thermodynamically stable form; right?
A. Yes, I think that's true, that that's an obvious choice for formulation.
Q. So the specification of the crystalline malate salt patents disclose the polymorphic form that a person of skill would look to first; right?
A. Yes, they are the most thermodynamic stable form that we know of, would certainly be an option for formulation unless there was some issue such as very low solubility.
Q. And the reason why a person would look for that most thermodynamically stable form first is because it's typically the starting point for development because of the possibility that other polymorphs may convert to the most stable form; right?
A. Yes, that's correct.
Q. And the choice of a less stable form is less common and would typically be made to overcome a specific disadvantage inherent in the most stable form; right?
A. Yes, I think that's true.
Q. And you haven't offered any opinion identifying any specific disadvantage inherent in the N-1 and N-2 forms; right?
A. No, I don't think I have.

12:19:46 Q. In fact, to the contrary, you showed Your Honor that the specifications of these patents expressly describe the favorable stability properties of the N-1 and N-2 forms; right?
12:19:56 A. Correct.
12:19:57 Q. So a person of skill would understand from the specification that the N-1 and N-2 are highly stable forms; right?
12:20:05 A. Yes, I believe that's true.
12:20:06 Q. Now, as of the priority date, a skilled person could typically use a microscope to determine if a solid was crystalline; right?
12:20:15 A. Typically, yes. A polarizing microscope would be a way to do that.
12:20:20 Q. You could also do it with XRPD; right?
12:20:22 A. That's right. That would be perhaps the most common.
12:20:24 Q. You could also do it with DSC; right?
12:20:27 A. You can certainly measure a melting point which would indicate there was something crystalline there, yes.
12:20:33 Q. And so a person of skill could use a microscope, XRPD, DSC to identify crystalline material; right?
12:20:40 A. You can't always use DSC and a microscope to establish definitively if something is crystalline.
12:20:46 Q. But you can; right?
12:20:47 A. Typically, but not always. It --

Q. You -- and you showed Your Honor --
A. It depends on the material.
Q. Sorry.
A. It depends on the material.
Q. And you showed Your Honor that the specification of the crystalline malate salt patents disclose using XRPD and DSC to disclose crystalline -- to identify crystalline material; correct?
A. To characterize the material of which the X-ray diffraction is really the one that's relevant to the crystallinity.
Q. And you could identify that it's crystalline without identifying its form; right?
A. In some cases, but not all.
Q. Now, let's talk more about polymorphs. As of the priority date, you agree that polymorph screens were well known; right?
A. Yes.
Q. And a polymorph screen involves running experiments in parallel to search for different polymorphs of a compound; right?
A. Yes.
Q. And you have offered the opinion that such screens are routine procedure; right?
A. Correct.

Q. It's your opinion that such a screen takes no more than a few weeks; right?
A. That's right.
Q. And it's your opinion that such a screen is highly effective at identifying polymorphs; right?
A. Yes, it is, but not all possible polymorphs, of course.
Q. You say that stable forms of a polymorph would have been readily identified by a person of skill as of the priority date; right?
A. Yes, that's true unless there's an issue with something like ritonavir where there's difficulty in the nucleation.
Q. And it's your opinion that a person of skill who was aware of cabozantinib would also have been motivated to identify the pharmaceutically relevant polymorphs; right?
A. Yes, I think that's true.
Q. And you've offered the opinion that such an effort to identify the pharmaceutically relevant polymorphs of cabozantinib, that would be routine; right?
A. Yes. You could undertake a routine polymorph screen and certainly identify, you would hope, some solid forms, but not all.
Q. And you've also offered the opinion that a person of skill could identify them with a reasonable expectation of

success; isn't that true, sir?
A. Yes, but not all of them, not the full scope.
Q. Now, let's talk a little bit about those forms as you showed the Court earlier today. None of those forms were identified as of the priority date of the crystalline malate salt patents; correct?
A. That's correct.
Q. They all came after; right?
A. Yes.
Q. Now, if we go to -- actually we'll come back to that.
You've offered the opinion that a little over -- strike that.
You've previously offered the opinion that a little over half of molecules are polymorphic; correct?
A. Yes. I think that's what the statistics say.
Q. And so that means for half of all molecules there's only one form; right?
A. That we know of so far, that's right.
Q. And for the other half, it can range up to at most 14 pure polymorphic forms; right?
A. Pure in the sense of characterized by single crystal crystallography. For things like atorvastatin, calcium and --
(Reporter clarification.)
THE WITNESS: Sorry. For things like

atorvastatin, calcium, it's 70-plus forms.
BY MR. PRUSSIA:
Q. We'll come back to that, but typically they can range up to 14 pure polymorphic forms; right?
A. So that's the raw example where there are well established single crystal structures. That's a very high standard of characterization.
Q. So I think before you took the stand Your Honor asked you how many times you testified before him, and I think you said three, right?
A. To my recollection.
Q. One of those was in the Entresto trial; right?
A. Correct.
Q. And I believe Your Honor asked you specifically -- and we can pull it up -- "What do you as a solid state chemist -- solid state chemist expect in terms of the number of polymorphic forms of a particular compound or even a supramolecular complex?"

And then there was some back and forth, and you said, "Well, for obviously half it's just one, but it can range all the way up to 14 pure forms of a molecule, for example."

That's what you told Judge Andrews in the Entresto case; right?
A. That's correct, and that's pure forms so that's not

including solvates.
Q. That was my question, sir. My question to you about a minute ago was, for the other half, it can range up to 14 pure polymorphic forms; right?
A. Yes.
Q. Okay. Now, the number of polymorphs is quite dependent on the system; right?
A. Yes. That's certainly true, and the amount it is studied.
Q. And here, cabozantinib has been studied for 14 years; right?
A. I believe so, yes.
Q. Four different pharmaceutical companies have looked at it; right?
A. Sorry?
Q. As far as you know?
A. Yes.
Q. So Exelixis has; right?
A. Correct.
Q. MSN has; right?
A. Correct.
Q. Mylan and Cipla have, too; right?
A. Yes.
Q. And no one has identified any solvate form of cabozantinib; right?

12:25:30 A. Identified what? Sorry.
12:25:31 Q. Any solvate form of cabozantinib; right?
12:25:33 A. Yes, they have. I think we discussed it at my
12:25:36 deposition that the TGA weight loss is indicating a solvate
12:25:39 form.
12:25:40 MR. PRUSSIA: So, let's pull up Volume I, Tab 6.
12:25:51 Deposition 153, Line 11 to 15.
12:25:55 The question -- the question was: "Are any of
12:25:59 Mylan M-1, M-2, M-3 and M-4 solvate forms?"
12:26:04 "ANSWER: Yeah. I don't know as I sit here
12:26:05 today. I could look at the data again, but I didn't address
12:26:08 that. Correct."
12:26:09 MR. COOPER: Objection, Your Honor. This is
12:26:11 incomplete. Later in the deposition, his recollection was
12:26:13 refreshed and he discusses.
12:26:14 MR. PRUSSIA: You can do that on redirect. This
12:26:15 is -- that was the question. This was his answer.
12:26:17 THE COURT: So, do you have the citation of
12:26:19 where else this occurred?
12:26:24 MR. COOPER: Yes, at 328 there's a discussion
12:26:32 about the figure that -- we're discussing here 328 starting
12:26:36 at 22 and going over to 329:11.
12:26:41 THE COURT: All right. So why don't you just
12:26:42 bring that up later because the answer here is he doesn't
12:26:44 know. And because he hasn't looked at it -- so I don't

understand why -- how that really impacts anything.

BY MR. PRUSSIA:

Q. So we can move on. An XRPD diffractogram of a material indicates it's crystalline based on the presence of peaks; right?

A. Yes. That's right.

Q. Now, the trial last year, you told the Court that to differentiate polymorphic forms based on the XRPD diffractogram, a person of skill may need to identify the ten strongest peaks in the XRPD diffractogram?

A. Yes. That is the United States Pharmacopeia and the way in which a form is identified with respect to a reference.

Q. Right. So, again, my question was: To differentiate polymorphic forms, based on their XRPD diffractograms, a person of skill may need to identify the ten strongest peaks in the XRPD diffractogram; correct?

A. Yes, that's the USP way of doing it. Of course, even that's a shorthand for looking at the entire diffraction pattern, which whenever it's got ten peaks.

Q. Okay. But that was your testimony that you offered to Judge Andrews in the first trial; correct?

A. Yes, I think but that's within the context that I was describing it.

Q. Okay.

MR. PRUSSIA: Let's pull up DDX-20 from your demonstratives.

BY MR. PRUSSIA:

Q. In offering your opinions in this case for the Court today for form S, you only identify three peaks; correct?

A. These are the peaks that are listed in claims in MSN's patent, so these are the claimed peaks.

Q. You identify three peaks, not ten; correct?

A. I'm reciting claims of the patent. So MSN in their patent identified three peaks.

Q. And for form M-4, you identified four peaks not ten; correct?

A. Again, the claims list four peaks.

Q. And for form C-4, you offer nine peaks, not ten; correct?

A. Again, these are claimed peaks that are recited in the patent claims.

Q. And for one of those peaks for C-4, it overlaps with form N-2; right?

A. Yes, that's not uncommon for there to be a peak, as I explained.

Q. Now, just a couple questions and then we're I think almost done.

With respect to form S, you're not offering the opinion that form S is an unstable form; correct?

A. Just repeat the question, please.
Q. Sure. With respect to form S, you're not offering the opinion that form S is an unstable form; correct?
A. So, we discussed this at my deposition. Stability is always with respect to a particular set of circumstances. So, it's not unstable under ambient conditions. But obviously, as I said to you at the deposition, it would be unstable if there's a melting point.
Q. And a high -- a hygroscopic polymorph is not always more unstable than a nonhygroscopic polymorph; right?
A. Yes, that's right. Not -- not by definition, although often that's the case.
MR. PRUSSIA: No further questions, Your Honor.
THE COURT: All right. Thank you, Mr. Prussia.
Mr. Cooper, any redirect?
MR. PRUSSIA: Your Honor, I do need to move in a few exhibits. Sorry, Bryce.
It's PTX-322, PTX-610, PTX-265, PTX-333, and PTX-327.
MR. COOPER: No objection.
THE COURT: No objection. All right. Thank you. Admitted without objection.
(PTX Exhibit Nos. 322, 610, 265, 333, 327 were admitted into evidence.)

REDIRECT EXAMINATION

BY MR. COOPER:

Q. Now, Dr. Steed, you spent some time on cross-examination talking about various other potential counterions that a POSA might consider putting in a salt screen for cabozantinib.

Do you recall that?

A. I do.

Q. And counsel asked you a number of questions about hydrochloride, do you recall that?

A. Correct.

Q. Is hydrochloride the most common counterion or common salt that's been FDA approved?

A. Correct.

Q. Now, are you offering any opinion that a POSA would not include hydrochloric acid in a salt screen for cabozantinib?

A. No, I'm not. That's an obvious one to include.

Q. And how many different counterions does a POSA include in a typical salt screen?

A. Around 15 to 20.

Q. And counsel showed you the chart from Bighley, do you recall that?

A. Yes.

Q. And he pointed you to hydrochloride; is that right?

A. Correct.
Q. Are there any other salts or anions on that chart, to your recollection, that are over 6 percent, other than hydrochloride?
A. Not to my recollection, no.
MR. COOPER: Can we pull up PDX-9.3?
(Discussion held off the record:)
MR. COOPER: PDX. PDX-9.3. Thank you.
BY MR. COOPER:
Q. Okay. Counsel asked you some questions about this chart. Do you see that -- do you recall that?
A. Yes.
Q. All right. And, again, he focused on chloride.
Dr. Steed, do you see the besylate salt -- salt on this list from Bighley?
A. Mesylate?
Q. Besylate.
A. Besylate. I do not -- oh, yes, I do, right at top.
Q. It's a tiny sliver up at the top.
A. I see it.
Q. And do you see that it was used four times, as reported in Figure 2 of Bighley?
A. Yes.
MR. COOPER: And now can we pull up PDX-9.5? Thank you.

BY MR. COOPER:
Q. And counsel asked you some questions and pulled out a paragraph from 399 on -- from your expert report. Do you recall questions on that this?
A. I do.
Q. Now, paragraph 399 is discussing a number of salts that were identified, that we talked about on direct, that were non-toxic; is that right?
A. Correct.
Q. Now, is paragraph 399, is that expressing your opinion of the salts that a POSA would include in a salt screen for cabozantinib?
That is -- does paragraph 399 represent an opinion from you about the scope of all of the salts that would be included in a cabozantinib salt screen?
A. No, it doesn't.
Q. And so what exactly are you just saying in paragraph 399?
A. This is part of the logic of whittling down, the organic salts listed, to what a person would regard as obvious to include.
Q. And so, just to be clear, paragraph 399 does not represent a final list, as counsel described it, of the salts that you would include in a cabozantinib salt screen; is that right?

A. Correct.
Q. Counsel -- speaking of other salts, counsel also showed you -- thank you.
Counsel also showed you PTX-265. And this is a -- an Exelixis patent; is that right?
A. Correct.
Q. And what is the publication date of this Exelixis patent?
A. May 26th, 2022.
Q. Okay. So is this prior art?
A. No.
Q. Would a POSA have been aware of this as of the priority date?
A. They would not have.
Q. Would a POSA have considered anything in this reference as of the priority date?
A. No.
Q. And counsel asked you some questions about essentially the predictability of identifying properties of salts before a salt screen is run, do you recall that line of questioning?
A. I do.
Q. And specifically he referred to the Black reference that quoted something to the effect that it was -- it is essentially nonexistent -- the ability is essentially

nonexistent to identify the properties in advance of running the salt screen.

Do you recall that?

A. I do.

Q. Is that inconsistent with anything you've said so far today?

A. No, not at all. You wouldn't know the outcome of the salt screen before you did it, otherwise you wouldn't need to do it.

Q. And counsel referred to some other properties that ultimately are measured for cabozantinib -- for a salt after a salt screen, including bioavailability, permeability.

Do you recall that line of questioning?

A. I do.

Q. And when would bioavailability and permeability and things like that be measured in the course of drug development?

A. Those are measured after the salt screen, further down the line.

Q. In the Exelixis asserted malate salt patents, is there any data about bioavailability or permeability of a crystalline cabozantinib malate salt that is ultimately put into a composition?

A. No, there isn't.

Q. Okay.

MR. COOPER: Turning to written description. The -- thank you. You can take that down.

BY MR. COOPER:

Q. You referred to the definition of crystalline, and counsel asked you some questions about that, do you recall?

A. Yes. In a layman's kind of definition.

Q. And you've said before that the definition is a crystal in which the crystal units are repeated; is that right?

A. Yes.

Q. Now -- and you talked about this on your direct, you showed a slide, but can the repeating crystalline units, the unit cells be different from one crystalline form to another?

A. Yes. That's what makes them different crystalline forms. They have a different unit cell, a different underlying packing arrangement.

Q. And counsel asked you some questions about whether the asserted claims require all of the cabozantinib crystalline (L)-malate forms, do you recall that?

A. I do.

Q. Now, are you giving an infringement opinion in this case?

A. No, it's a legal term. I am not a lawyer, so I'm not -- I'm certainly not giving an infringement opinion.

12:37:17 Q. Okay. So then could -- for written description, can you describe as far as what crystalline cabozantinib malate salts fall within the scope of the asserted claims?
12:37:25 A. Yes, within the scope of the asserted claims, it's my opinion that the -- all crystalline cabozantinib (L)-malate salts fall within that scope.
12:37:34 Q. And counsel asked you some questions about whether the specification discloses a way to make a crystalline cabozantinib (L)-malate salt.
12:37:43 Do you recall that discussion?
12:37:45 A. I do, yes.
12:37:47 Q. And does the -- and you said that a POSA could run a polymorph screen and could routinely potentially identify more.
12:38:01 Do you recall that line of questioning?
12:38:02 A. Yes, potentially.
12:38:03 Q. Now, you -- are you giving an enablement opinion at trial today?
12:38:07 A. No.
12:38:10 Q. Did Exelixis run a polymorph screen in the course of their development?
12:38:13 A. Yes, they did. And that polymorph screen revealed only the N-1 and N-2 forms.
12:38:23 Q. And counsel asked you some questions about whether all crystalline cabozantinib malate salts have the same

chemical formula and chemical makeup, and you said yes.

Do you recall that testimony?

A. They do unless they're solvates.

Q. And -- but do all crystalline cabozantinib (L)-malate salts have the same crystalline structure?

A. No, no, they don't. They're all --

Q. Do they all have the same physical properties?

A. No.

Q. Do they all have the same chemical properties?

A. No.

Q. Do they all have the same functional properties?

A. No.

Q. Counsel also asked you some questions about whether the form N-1 and N-2 are the most pharmaceutically relevant crystalline cabozantinib salts.

Do you recall that line of questioning?

A. Yes, I do.

Q. Is there anything in the claims of the asserted patents that are limiting the scope of the asserted claims to pharmaceutically or most pharmaceutically relevant crystalline cabozantinib malate salts?

A. No, nothing at all.

Q. Is there anything in the asserted claims that limit them to the most thermodynamically stable or most common thermodynamically stable salts?

A. No, there isn't.

Q. Is there anything in the asserted the claims that limit them to crystalline cabozantinib malate salts with any particular properties?

A. No, there isn't. It's address -- it addresses all of them.

Q. And counsel asked you some questions about whether you could identify whether a sample of a -- of a cabozantinib malate salt was crystalline or not without doing XRPD testing and further types of testing.

Do you recall that line of questioning?

A. I do.

Q. Now, but whether it has been identified or not, is a crystalline cabozantinib malate salt still existing in a crystalline packing arrangement or form regardless of whether or not you have measured it yet?

A. It is, yes. It can't be crystalline without actually having an underlying crystal structure and the characteristics of that crystal structure or crystal form.

Q. You -- he also asked you about some testimony you gave to Judge Andrews, and he quoted you about saying a POSA may have to review at least ten peaks.

Do you recall that?

A. Yes.

Q. Now -- and we looked at your chart again where you

called out the claimed peaks for each of the crystalline cabozantinib malate salts.

Do you recall that?

A. Yes.

Q. And what was the data on the right-hand side? Why did you select that for the chart?

A. That's because those are the peaks that the authors of those documents chose to claim in their claims.

Q. And did you look at not only those claims, but did you look at the entire diffractograms for each of those crystalline cabozantinib salts?

A. I certainly did. That's the best practice, to look at the entire diffraction patent.

Q. And is that what a POSA would do?

A. Yes.

Q. And what was your conclusion after looking at the entire scope of the diffractogram?

A. Looking at the whole diffraction pattern, it's clear these are different forms to each other.

Q. And counsel also asked you some questions about some testimony you gave confirming that one of the -- or the most pure crystal structures that have been categorized is 13.

Do you recall that?

A. Yes. I think it's 14 now.

Q. Fourteen. And there was some back and forth about

what pure meant in that context.

Could you explain that?

A. Yeah. So that -- that discussion was around non-solvated polymorphs. I think the most that we know of is 14 now. Once you -- once you start about solvates, then there are more forms. I mentioned earlier Atorvastatin example, which the literature says is around 70.

Q. And counsel referred to some testimony you gave at trial last year. Do you recall testifying in front of Judge Andrews last year that the MSN S form is a hydrate?

A. I do. Yes.

Q. Okay.

MR. COOPER: No further questions, Your Honor.

THE COURT: All right. Thank you, Dr. Steed. You may step down.

THE WITNESS: Thank you.

THE COURT: All right. Let's take a lunch break of an hour, and I will see you again after the hour is up.

DEPUTY CLERK: All rise.

(Luncheon recess was taken.)

DEPUTY CLERK: All rise.

THE COURT: All right. Everyone be seated.

MR. COOPER: Your Honor, we have some exhibits to move in from the last exam.

THE COURT: Sorry. What now?

MR. COOPER: We have some exhibits to move in from the last --

THE COURT: All right. Sorry.

MR. COOPER: Some of these may have been moved in before, so... But for completeness: JTX-1, JTX-2, JTX-3, JTX-9, JTX-10. DTX-558, DTX-177, DTX-243, DTX-392, DTX-191, DTX-170, DTX-20, DTX-333. PTX-256. DTX-222, DTX-121, DTX-13, DTX-167. PTX-610. DTX-180, DTX-192, and DTX-166.

MR. PRUSSIA: No objection, Your Honor.

I just have one additional from our side.

THE COURT: All right.

MR. PRUSSIA: That flip chart is going to be marked as PDX-9.13.

We're taking a picture for the Court.

THE COURT: That seems really pointless.

MR. PRUSSIA: It's not being offered for evidence, Your Honor.

THE COURT: Well, you know, there was -- so I'm going to deny that.

MR. PRUSSIA: Okay.

THE COURT: It's pointless.

(JTX Exhibit Nos. 1, 2, 3, 9, and 10, were admitted into evidence.)

(DTX Exhibit Nos. 13, 20, 121, 166, 167, 170,

177, 180, 191, 192, 222, 243, 333, 392, and 558 were admitted into evidence.)

(PTX Exhibit Nos. 256 and 610 were admitted into evidence.)

THE COURT: All right. So what's now?

MS. GRDEN: Good afternoon, Elizabeth Grden from MSN. We would like to play a video now from the March 9th, 2023, deposition of Dr. Jo Ann Wilson. She's the former vice president of chemistry manufacturing and control.

THE COURT: And just to remind me, Doctor -- this is going to -- because I remember the Plaintiffs talking about her in opening, or at least I thought they did.

This is going to cover everything she's ever going to testify about in this trying; right?

MS. GRDEN: This is everything the parties would say like to present for her testimony.

THE COURT: Yeah. Okay.

MS. GRDEN: She is one of the two inventors of '349 patent. We will be offering certain exhibits into evidence. With your permission, I'll hand those up.

THE COURT: All right.

MS. GRDEN: And those exhibits will be 291 -- DTX-291, which is identified in the deposition as Exhibit 8.

PTX-35, which is identified as Exhibit 6. And PTX-10, which is identified as Exhibit 7.

The time allotment: MSN, 9 minutes 13 seconds. Exelixis, 8 minutes, 28 seconds. And 18 seconds of joint testimony.

(Beginning of videotape deposition excerpt.)

Q. Could you state your full name for the record?
A. Jo Ann Zbur Wilson.
Q. And you joined Exelixis in December of 2002; right?
A. Correct.
Q. And at Exelixis, you served as a senior director from 2002 to 2004, and then a vice president of chemistry, manufacturing and controls from 2004 to 2014; is that right?
A. That's correct.
Q. Okay. What CMC activities were you responsible for in support of Cabometyx?
A. We had started developing the tablet formulation for cabozantinib when I was employed by Exelixis, but I left the company before that product was launched.
Q. And so were you involved in selecting the synthetic route to prepare cabozantinib for use in potential capsule and tablet -- tablet formulations?
A. I was involved in evaluating the medicinal chemistry route that was used to manufacture XL184, as it was known at the time, and then the process optimization and, you know,

01:45:47 modifying that synthesis route to what, eventually, became the commercial route for the manufacture of cabozantinib (L)-malate.
01:45:58 Q. Okay. And so the -- the medicinal chemistry route that you referred to, that -- was that the first synthetic route that Exelixis developed for manufacturing cabozantinib?
01:46:06 A. Yes, that's correct, for -- for producing small quantities of XL184.
01:46:16 Q. Did you have any role in determining what excipients would be used for cabozantinib capsule and tablet -- tablet formulations?
01:46:25 A. Yes, I did.
01:46:26 Q. And could you describe what your roles and responsibilities were in that regard?
01:46:29 A. Well, I oversaw the activities that were required for developing the initial capsule formulation through my formulation development group and the CDMO that we were working with for manufacturing the -- the early batches for -- for the clinic through the commercial batches.
01:46:50 And then, as I mentioned to you earlier, we had started developing the tablet formulation. I was involved in the -- through management of my formulation development group and oversight of them and their activities, the development of the tablet formulation as well.

Q. Are formulation scientists in the field generally motivated to minimize genotoxic impurities in drug products as much as they can?

THE WITNESS: Yeah, I can't speak in general terms. I can tell you what we did at Exelixis.

Q. And in your experience, is -- is minimizing genotoxic impurities in drug products as much as possible important?

A. Yes, I believe it is.

Q. And what did you rely on when developing GTI control strategies? Is that something that you consulted scientific literature for? Relied on your experience as a person in the field? Just generally.

A. Well -- pardon me -- at the time that we were doing this with respect to cabozantinib, there was a draft guidance from the FDA, the one that you -- that we mentioned previously, regarding potential genotoxic impurities. And we used that guidance to direct our activities towards the GTI control strategy.

Q. To -- to your knowledge, did anyone at Exelixis or at the direction of Exelixis ever prepare a crystalline form of cabozantinib (L)-malate other than N-1 or N-2?

THE WITNESS: No not to my knowledge, no.

Q. Doctor, do you recognize Exhibit 6 as Section 6 from the Exelixis NDA for cabozantinib capsule products?

A. I believe this is Section 3.2.S.2.6 of the NDA for

01:48:44 cabozantinib capsules.
01:48:46 Q. Now, were you involved in designing the Process A or
01:48:50 Process B synthetic routes for the API?
01:48:54 A. Process A is this -- is the synthesis group that was
01:49:00 used by medicinal chemistry. So A and B refer more to the
01:49:05 synthetic route processes, the actual conditions that were
01:49:10 utilized for execution at each step going from, you know, A
01:49:15 to B to C to D, if you will. So Process A was initially
01:49:20 used by Exelixis' medicinal chemistry to make small
01:49:24 quantities of XL184.
01:49:27 And then, when the compound got moved over into
01:49:33 development status, my group took over and we did all the
01:49:38 subsequent process development around Process A and then,
01:49:42 ultimately, Process B.
01:49:45 Q. And API batches made by Process A were used in both
01:49:49 non-clinical and initial -- initial clinical studies by
01:49:53 Exelixis; is that right?
01:49:54 A. That's correct.
01:49:56 Q. And Process B was developed as the synthetic route
01:50:00 that was ultimately used for the commercialized Exelixis
01:50:04 products; correct?
01:50:05 A. That's correct.
01:50:07 Q. What -- approximately, what was the time frame of
01:50:09 process A-1 when it was developed?
01:50:11 A. That was early on in the development. I believe that

01:50:17 we made our first batch of XL184 using Process A-1 in 2004, and we moved away from Process 1 shortly thereafter.

01:50:33 Q. The second version of Process A, known as Process A-2, was developed and used by Exelixis for non-clinical safety studies and also for use in the clinical program; correct?

01:50:44 A. That's what it says, yes.

01:50:47 Q. So as far as the synthetic route for process A-2, that was something that Exelixis developed and provided to their contract organizations; correct?

01:50:57 A. Correct.

01:50:59 Q. And on this page, in Section 6.4.2.2.1, there's a -- it says "key issues identified with Process A-2."

01:51:11 Do you see that?

01:51:12 A. I do.

01:51:15 Q. And in the first bullet it says, "the competing" -- in the third sentence, "The competing decomposition pathway of XL184-1-3" to that impurity 1-1 "under the reaction conditions could not be controlled."

01:51:32 Do you see that?

01:51:33 A. I do.

01:51:36 Q. Could you explain?

01:51:37 A. Yes. So when -- when 1-3 is formed in -- one of the competing side reactions, undesirable side reactions, is the -- the decomposition of XL184-1-3 to form XL184-1-1.

01:52:00 Q. And so after process A-2, Exelixis developed Process B; correct?
01:52:04 A. Correct.
01:52:06 Q. If you recall, or could you describe the genotoxic impurity assessment that was performed by BMS?
01:52:13 A. In general terms? Yes.
01:52:16 Q. In general.
01:52:17 A. Yeah. So in accordance with the draft guidance by the FDA, an assessment of all starting materials, intermediates, impurities, and potential impurities were evaluated in an in silico computational model that can be predictive of the outcome of bacterial genotoxic -- or bacterial mutagenicity assays. And then compounds that were flagged as containing structural alerts were then evaluated in said bacterial mutagen -- mutagenicity assays to either confirm or not whether or not these impurities had a potential to be genotoxic.
01:53:08 Q. And this section on this page describes the commercial process B-2, correct?
01:53:12 A. Correct.
01:53:16 Q. And it states that process B-2 evolved from process B-1 to better control the final crystal form and to better control the GTI levels; right?
01:53:25 A. That's correct.
01:53:26 Q. In the third paragraph in this section, it begins,

01:53:35 "Process improvements with respect to reaction temperature, volumes and reagent charge quantities were made to the cabozantinib free base process."

Do you see that?

A. I do.

Q. Is changing reaction temperature -- was that a well-known strategy to try to minimize levels of GTIs?

THE WITNESS: So minimizing the level of, you know -- and GTIs, you know, we're talking about four that were identified, and they have -- they have -- they are introduced at various stages in the manufacturing process. They're removed or purged at various stages of the manufacturing process, so you -- I can't just lump them all together and speak of GTIs.

In particular, what we were concerned with here was the GTI 1-1 because it was a degradation product. And so the things like temperature, volumes, reagent charges required a very intimate knowledge of the chemistry. So it's not just something with a broad brush that you can say, "Oh, I'm going change the reaction temperature, and that's going to, you know, reduce the GTIs."

So this was -- this is a -- this was one sentence that sort of encompasses an incredible amount of work that was done to be able to come up with a final process that would, you know, give us the -- the API with

01:55:04 the levels of 1-1 that we were striving for.
01:55:07 Q. And the next sentence, it says, "A recrystallization step was introduced in order to minimize the levels of GTIs."
01:55:14 Do you see that?
01:55:15 A. I'm sorry. Which paragraph again?
01:55:18 Q. Still in that third paragraph, the second sentence.
01:55:23 Could you explain how recrystallization reduces GTIs?
01:55:27 A. Well, remember, recrystallization is the technique that's used to purify solid crystalline materials. So it's -- it is -- it is generally -- the general principle of that is that, you know, once you do a recrystallization, that the -- that the solid that crystallized -- so you take a solid. You take it up into solution, usually with heat, to get a complete solution. And then when you cool it down, the -- the compound, you know, that you're looking at crystallizes out.
01:56:02 And the idea is, is that impurities would stay in the liquid portion. So that's kind of the general principle of purification, in general, by recrystallization.
01:56:13 Q. Was recrystallization a known method to reduce genotoxic impurities from API at the time that you were developing this process?
01:56:27 THE WITNESS: So recrystallization is a

procedure that's used to purify solids, whether it's from GTIs, regular impurities. So it can be used to -- to remove genotoxic impurities if it's -- you know, but it's not necessarily going to do that. So it's not just, you know, that simple.

Q. All right. Doctor, do you recognize Exhibit 7?

A. I recognize this, yes.

Q. And what is this document?

A. This appears to be -- this appears to be information from an IND.

Q. Can you turn to the page that ends Bates No. 969.

And Section 7.2.2.1 here identifies the manufacturer of several batches of API, correct?

A. Correct.

Q. Figure 7.2-8 provides the synthetic route for the preparation of the API that was produced in Lot No. P172-27-1 and used in that phase 1 clinical study, correct?

A. Correct.

Q. Do you recognize Exhibit 8 as an international publication with the number W0 2010/083414?

A. Yes, that's -- that's what it says, yes.

Q. And this is a -- this is an international publication where the applicant is Exelixis.

Do you see that?

A. I do.

01:58:18 Q. And the inventors are Adrian St. Clair Brown, Peter Lamb, and William Gallagher, correct?
01:58:24 A. That's correct.
01:58:25 Q. Can -- if I call this the Brown reference, are you okay with that?
01:58:29 A. Yes, of course.
01:58:31 Q. And Example 1 is directed to preparation of cabozantinib and the (L)-malate salt thereof, correct?
01:58:37 A. Correct.
01:58:38 Q. And compound -- the cabozantinib (L)-malate salt is referred to as Compound I in this publication, I believe; is that correct?
01:58:47 A. That's what it says.
01:58:49 Q. And Scheme 1 provides a synthetic route for the preparation of cabozantinib (L)-malate, correct?
01:58:56 A. Correct.
01:58:58 Q. And looking at this route -- the synthetic route for preparing cabozantinib (L)-malate that's in the Brown reference is the Exelixis process A-2 that we discussed earlier, correct?
01:59:08 A. Correct. Yeah. So this -- the syn- -- Exelixis used the synthetic process here that's identified in the Brown reference in order to prepare the API Lot No. P172-27-1 that we saw in Exhibit 7; is that right?
01:59:28 THE WITNESS: This synthesis route here

01:59:33 (indicating) and what appears to be described here, yes,
01:59:34 is -- is -- looks to be the route that we used to prepare
01:59:37 that lot.
01:59:39 Q. What about adding purification steps, is that a known
01:59:42 way to potentially reduce genotoxic impurities?
01:59:47 THE WITNESS: It's a way that could be used to
01:59:49 reduce the level of genotoxic impurities.
01:59:54 Q. And was it known at the time that quinoline compounds
02:00:05 could be potentially mutagenic?
02:00:08 A. Well, I -- I believe that there were a lot of
02:00:13 examples in the literature of quinoline compounds being
02:00:18 mutagenic, but I'm not a toxicology expert, so I can't say
02:00:23 for sure.
02:00:26 Q. Okay. You don't recall any other HPLC methods that
02:00:29 had a higher limit of detection that you used for this
02:00:31 project than 0.02 percent --
02:00:34 A. I'm sorry.
02:00:36 Q. -- is that right?
02:00:37 A. I -- I don't -- 0.02 percent is pretty much the
02:00:42 standard LOD for an HPLC method.
02:00:46 Q. Okay. Is the limit of quantification for HPLC, is
02:00:52 the -- is that -- is the standard 0.05 percent?
02:00:56 A. That seems to be pretty standard, yes.
02:01:02 Q. Was Exelixis' goal in its process development to
02:01:06 reduce the level of 1-1 impurity by as much as it could?

A. So the goal -- it was twofold. I -- I'll answer your question with regard to the drug product, to this tablet formulation.

The goal was not to increase the level of 1-1 more than what was already present in the incoming API batches.

Q. Got it.

And did Exelixis also have a goal at the outset of its process development to ensure that the API and drug product exhibited little to no increase in genotoxic impurity levels during long-term storage?

A. Yes.

Q. Now, does the work that resulted in your '349 patent in Exhibit 4, can you distill that down to one step?

A. No.

Q. Why not?

A. It was a -- a lot of work. So I -- I was referring to the number of steps in the synthesis scheme, which is quite different than the process. In -- the time that it took going from Scheme 1, which is process A, to the point where we came up with the final commercial process was a time that spanned eight years. So it was much more complicated than just reducing one step out of the synthesis sequence.

(Conclusion of videotape deposition excerpt.)

MS. GRDEN: Your Honor, we'll now play video from the August 11th, 2021, and March 23rd, 2023, depositions of Peter Lamb, executive vice president, scientific strategy, and chief scientific officer of Exelixis, and named inventor of the '439, '440, and '015 patents. And in connection with Mr. Lamb's testimony, MSN will be offering DTX-035, if I can hand those up.

THE COURT: Okay.

MS. GRDEN: The time allotment is MSN, four minutes, 51 seconds; Exelixis, six minutes and 13 seconds.

THE COURT: Okay.

(Beginning of videotape deposition excerpt.)

Q. Okay. You understand, sir, that you've been designated by Exelixis to give testimony on behalf of the company today?

A. Yes, I understand with respect to certain designated topics.

Q. Okay. Can you tell me why Exelixis decided to do a salt screen through Pharmorphix?

A. Yeah, so, you know, it is important, as we're advancing a compound towards the clinic and, ultimately, commercialization, to identify a suitable solid state form for the drug. There were multiple options, it's my understanding, of what that form can take, and it differs in an unpredictable way depending upon the compound. A salt

02:04:24 screen is one process that you can use to help identify
02:04:27 potentially suitable forms, suitable solid state forms, so
02:04:32 that's the rationale for proceeding with one form.
02:04:38 Q. Do you know who the kind of key contact at Exelixis
02:04:42 was with Pharmorphix beginning in 2004?
02:04:46 A. I don't think I could say who the key contact was
02:04:49 with certainty.
02:04:52 Q. Do you know anybody who was in contact with them?
02:04:54 A. I suspect John Nuss, who was the head of medicinal
02:04:59 chemistry at the time, was the contact.
02:05:02 Q. Okay. What were your contributions to Claim 1?
02:05:05 A. So when we received the initial report on the salt
02:05:12 screen from Pharmorphix, with the 22 counterions, I was -- I
02:05:19 reviewed that document in a meeting with Dr. Nuss, John
02:05:25 Nuss. We reviewed it, and we came to the conclusion or I
02:05:28 came to the conclusion that the (L)-malate salt was the best
02:05:32 salt to move forward.
02:05:35 MR. WARNER: Let's have Lamb Exhibit 10 on the
02:05:39 screen.
02:05:41 Q. And if you could have that available, sir.
02:05:45 MR. WARNER: I -- I think I said this. This is
02:05:47 EXEL68747 through 68789.
02:05:52 And have you seen this document before, sir?
02:05:55 A. I have, yes.
02:05:58 Q. Okay. This is a document from Pharmorphix called

02:06:06 primary salt screen on EXEL7184 for Exelixis, Inc. Correct?
02:06:12 A. That is correct.
02:06:15 Q. EXEL-7184 is the internal name for cabozantinib?
02:06:18 A. Yes, correct.
02:06:21 Q. And then if you go to the second page, the document
02:06:25 has a date of September 15, 2004. Right?
02:06:28 A. Correct.
02:06:31 Q. Okay. Now, you received this document on or about 15
02:06:36 September 2004?
02:06:36 A. Well, again, I saw this document in my meeting with
02:06:41 John Nuss. I don't recall the date of that meeting.
02:06:46 Q. Okay. It would have been after mid-September 2004?
02:06:50 A. Presumably.
02:06:54 Q. And so just to make sure I understand, did you have
02:06:57 any involvement with Pharmorphix prior to the time when you
02:07:00 first saw this report?
02:07:01 A. No, I didn't.
02:07:05 Q. And once the decision was made to have Pharmorphix do
02:07:09 a salt screen, you had no input into how it was going to be
02:07:12 conducted. Is that all fair?
02:07:13 A. That's fair, yes. I mean, we hired Pharmorphix
02:07:16 because they're experts in the field. It's -- you know,
02:07:19 solid state chemistry is a whole field in and of itself, not
02:07:22 something that we conducted internally at Exelixis at the
02:07:25 time, hence we went to experts.

02:07:30 Q. And I guess what I'm trying to understand is, is there a reason you just went forward with one opposed to, say, two or three?
02:07:38 A. Again, (L)-malate salt looked to be the one with the most desirable properties.
02:07:46 Q. Okay. How long did the process take you to evaluate this and choose the (L)-malate salt?
02:07:52 A. The meeting was somewhere between 30 minutes to an hour.
02:08:01 Q. Had you spent time reviewing the report prior to that? Prior to the meeting?
02:08:04 A. No. That was the first time I saw the report.
02:08:08 Q. Okay. So if I understand you correctly, you -- you got the report at some point after it issued, and over the course of a 30- to 45-minute meeting with John Nuss decided that the (S)-malate was best?
02:08:20 A. 30 to one hour meeting. But yes.
02:08:23 Q. To one hour?
02:08:25 A. Yes.
02:08:25 Q. Okay. All right. And so Exelixis decided to pursue the (L)-malate form of cabozantinib for further pre-clinical development based upon your recommendation and decision; is that right?
02:08:36 A. That's correct, yes.
02:08:37 Q. And I -- I understand that your recommendation and

02:08:41 decision was based on your review of the results of the salt screen conducted by Pharmorphix; is that right?

02:08:49 A. That's partly right. So that played a -- you know, played a big role in it for sure. We had the data from Pharmorphix in that -- in that time frame. They had identified and characterized a number of different salts, a number of which were crystalline and had been scaled up.

02:09:06 Looking at that report, it certainly, you know, suggested to me that the (L)-malate salt looked like a very promising candidate to take forward. But beyond that, there was some additional testing that was done on the malate salt before the final decision was made.

02:09:25 Q. What additional testing was that?

02:09:30 A. Yeah, I would say, you know, one of the main pieces of testing was called an in vivo pharmacokinetic experiment. So what we did, we actually -- I think I took -- took four of the salts, including the L -- the (L)-malate. And we dosed them to -- to animals, it was rats.

02:09:49 I would say the most crucial part of that experiment was we actually administered what we called a solid oral dosing form, which essentially was solid cabozantinib (L)-malate put into little -- little capsules that were then administered to the rats, sort of the closest thing that we could get to on the pre-clinical side to, you know, how you would actually dose people, ultimately.

02:10:08 So what we were looking for, you know, with the malate salt, and you know, we also did this with some of the other salts is, you know, will that solid drug actually dissolve either in the stomach or in the intestines of the animal and then actually get, you know, through the intestinal wall and into the bloodstream. So we were essentially looking for, you know, does the solid form of the salt have good oral bioavailability. And in the case with the (L)-malate salt, it did have -- it had very good oral bioavailability.

02:10:37 So there was that data. There was some additional data. I know we looked at the photostability of -- of the (L)-malate salt and a few other salts, again, just looking to see if it would break down in any way in the presence of lights.

02:10:50 THE WITNESS: Lights. Yeah, you'd much prefer to have a drug that is stable in the presence of light so you don't have to keep it in the dark all the time. So that was one piece of data.

02:11:00 We did do some broad screening of the solubility of the salts in -- in what we typically called various different matrices. You know, a lot of the early data on solubility that was done, and some of this was done at Pharmorphix as well, was just done in water. That's -- you know, that's -- you know, it's a piece of data that's --

02:11:25 that can be useful, but it's -- it's not the most relevant fluid in which to look at solubility.

02:11:31 There are things called simulated gastric fluids and simulated intestinal fluids that more try to mimic the kind of fluid environment that you actually find in -- in -- in people and in patients. So I know we did some assessment of the solubility in -- in those kind of fluids as well.

02:11:47 So it's that package of data which really got assembled in that -- in that sort of -- finally got assembled in that late July, early August period that led to the declaration of cabozantinib (L)-malate as the compound that we would advance into pre-clinical development.

02:12:04 Q. You -- you said a moment ago that the -- the in vivo rat studies included four salts. What were the four salts that were in the rat studies?

02:12:14 THE WITNESS: Yeah, from -- from memory, the (L)-malate was obviously one. There was the maleate, I believe, we tested. I want to say the hydrochloride, maybe the phosphate. There is a -- you know, if I'm -- you asked -- tech evidence document and want to refresh my memory, we can look there. It's -- there's also a report. But that's -- that's what I have from memory.

02:12:39 Q. Okay. And so the -- that in vivo data is presented or summarized in the technical evidence document?

02:12:47 A. That's correct, yes.

02:12:51 Q. The photosensitivity testing, is that also reported or summarized in the technical evidence document?
02:12:59 A. Yes, it is.
02:13:03 Q. And is the solubility, the -- the additional solubility testing also reported in the technical evidence document?
02:13:11 A. Yes, it is.
02:13:17 Q. Okay. And based on the -- the data in the Pharmorphix report, it was -- it was clear to you that the (L)-malate salt form was the -- was the salt to advance into pre-clinical development; is that right?
02:13:34 A. Well, I would -- I would put it as based on the Pharmorphix data, that the (L)-malate salt looked like a promising candidate. However, I would say that the -- for example, the PK experiments, I -- I outlined for you, you know, it was -- it was possible that we could have dosed solid cabozantinib malate and it would not be absorbed well, or it would not dissolve well, and therefore would have poor oral bioavailability. So we did need this additional data to make a final decision.
02:14:03 Q. And do you believe based just on the data in the Pharmorphix report that (L)-malate salt was the most promising salt based on the salt screen data?
02:14:14 A. Well, I said -- like I said, it looked like -- it looked like a promising candidate. And it was certainly one

that -- that I wanted to see characterized further.

But, again, no final -- no final decision could be made until we -- we'd really done that additional work. And as you saw, we carried forward not just the malate salt but a few of the others as well.

(Conclusion of videotape deposition excerpt.)

MS. GRDEN: Your Honor, we'd like to formally offer DTX-291, PTX-35, PTX-10, and DTX-35.

MR. PRUSSIA: I think 291 is already in but no objection.

MS. GRDEN: Sure.

THE COURT: All right. Admitted without objection.

(DTX Exhibit Nos. 291 and 35 were admitted into evidence.)

(PTX Exhibit Nos. 35 and 10 were admitted into evidence.)

MR. MATHAS: Your Honor, at this point, that is the end of our responsive case and we'll pass the case back over.

THE COURT: All right.

MR. PRUSSIA: Your Honor, Exelixis calls Dr. Khalid Shah.

THE COURT: Okay.

DEPUTY CLERK: Please state and spell your full

name for the record.

THE WITNESS: My full name is Khalid Shah, K-H-A-L-I-D, last name Shah, S-H-A-H.

KHALID SHAH, the witness herein, after having been duly affirmed under oath, was examined and testified as follows:

THE WITNESS: Yes, I do.

DIRECT EXAMINATION

BY MR. PRUSSIA:

Q. Good afternoon.

A. Good afternoon.

Q. Please introduce yourself to the Court.

A. My name is Khalid Shah.

Q. What is your educational background?

A. I have a BSC in pharmacy and I have a Ph.D. in pharmaceutics.

Q. Where do you work, Dr. Shah?

A. I work at Exelixis.

Q. What is your title at Exelixis?

A. My title is senior vice president of pharmaceutical operations and manufacturing and supply chain.

Q. What are your responsibilities?

A. My responsibilities include, obviously, in the commercial manufacturing of our drug products that are approved, Cabometyx, and Cometriq. I also oversee the

manufacturing of the active ingredient, cabozantinib. As well as all the raw materials for the commercial products. And I also oversee development of all new products, from the discovery stage all the way through to commercialization.
Q. What were your responsibilities --
DEPUTY CLERK: Can you try to slow down as best you can?
BY MR. PRUSSIA:
Q. What were your responsibilities with respect to preparing and submitting the new drug applications for cabozantinib?
A. So for cabozantinib specifically, I oversaw submission of the NDA, the complete NDA for Cabometyx. And I oversaw the drug product sections for the Cometriq submission and application.
Q. How long have you worked at Exelixis?
A. I worked at Exelixis for just over 14 years.
Q. When did Exelixis begin investigating potential tyrosine kinase inhibitors?
A. That would be in the early 2000s.
Q. How many compounds did the company investigate?
A. I would say about in the region of around 5,000.
Q. How many compounds did the company take into clinical trials?
A. Around 15.

Q. How many of those compounds were successful in those trials and ultimately approved by the FDA?
A. One.
Q. What is that approved compound?
A. That approved compound is cabozantinib.
Q. When was cabozantinib first approved by the FDA?
A. The initial approval was for the Cometriq submission in 2012.
Q. Has the compound received any additional approvals from the FDA?
A. Yes.
Q. When was that additional approval?
A. That was in 2016.
MR. PRUSSIA: Let's mark -- let's pull up PTX-4.
BY MR. PRUSSIA:
Q. This is Tab 1 in your binder, if you need it, Dr. Shah.
What is this document?
A. This is the prescribing information on package insert for Cometriq.
MR. PRUSSIA: If we go to PTX-1.
BY MR. PRUSSIA:
Q. This is Tab 2 in your binder, Dr. Shah, if you need it.
What is this document, Dr. Shah?

A. This is the prescribing information or package insert for Cabometyx.
MR. PRUSSIA: If we could turn, please, to Section 11.
BY MR. PRUSSIA:
Q. What is the active ingredient of Cabometyx?
A. So the active ingredient of Cabometyx is the cabozantinib (L)-malate salt.
Q. Now, the document makes reference to an (S)-malate salt.
What is that?
A. So the (S)-malate is just another designation for the (L)-malate salt. Just a different naming convention.
Q. You mentioned the word "salt." What is a salt?
A. Right. So at a really high level, a salt is where an ionizable compound, such as cabozantinib free base, is combined with a counterion, in this particular case, a salt. And the combination of the two together is what results in a pharmaceutical salt.
Q. What is the free base of the salt in Cabometyx?
A. That would be cabozantinib.
Q. And what is the counterion in Cabometyx?
A. The counterion is a malic acid.
Q. Now, did Exelixis initially pursue development of the free base of cabozantinib?

A. The free base was initially evaluated by Exelixis.
Q. And what did -- what conclusions did the company reach regarding the suitability of the free base?
A. Yeah. So after evaluation of the free base, Exelixis decided that it was not a form that would be developable and it exhibited a considerable amount of polymorphic instability in that it appeared to be able to convert to other polymorphs very readily.
Q. What do you mean when you say it exhibited polymorphic instability?
A. Yes. So what I mean by that is some polymorphs can be unstable and if certain polymorphs are unstable, they have the propensity to convert to other polymorphs and that's extremely undesirable.
Q. What were the risks of developing the cabozantinib free base?
A. There were considerable risks. You know, each -- polymorphs are characterized by different levels of solubility. So, if, you know, the free base were to convert to a different polymorph and that polymorph would have a different solubility, either higher or lower, you know, the risk is that the patient taking the drug could experience significantly higher amount of dose or lower amount of dose. The higher dose would be a safety issue and could cause harm and the lower dose would likely be subtherapeutic. So it

was a considerable concern.

Q. Did Exelixis try to develop a salt of cabozantinib?

A. Yes.

Q. What salt did Exelixis experiment with first?

A. So initially Exelixis used an HCl salt and that was simply for the purposes of dissolving cabozantinib in the vials, which were being used for the initial animal toxicity studies.

Q. Now, at some point did Exelixis investigate other salts?

A. Yes.

Q. And what did the company do to investigate other salts?

A. Yeah. So Exelixis partnered with a contract research organization called Pharmorphix and Pharmorphix performed a salt screen to identify additional salts.

Q. What is a salt screen?

A. So at a high level, a salt screen is a fairly complicated process whereby in order to attempt to form crystalline salts and multiple counterions of salt species are evaluated, different solvents are looked at and used in order to evaluate these counterion in an attempt to identify and form crystalline salts.

Q. How did Exelixis identify the best salts from the Pharmorphix salt screen?

A. Right. So Pharmorphix identified five of the most promising salt candidates and then Exelixis took those candidates through further evaluation and conducted PK animal experiments and looked at the in vivo bioavailability data and subsequent to all that work a final decision was made to progress the particular salt, which was the (L)-malate in this case.

Q. So, ultimately, what properties did Exelixis consider in deciding which salt to move forward with?

A. So, of particular importance was the solid-state stability of the (L)-malate salts, but also, more importantly, the in vivo bioavailability data that was generated in the animal species was considered to be of particular importance.

Q. So you mentioned bioavailability. What is that?

A. So, bioavailability is essentially when a tablet or capsule intended for oral administration, which is what cabozantinib is, is swallowed and travels down the GI tract, and the drug from the tablet or capsule will then be absorbed through what we call the epithelium layer, basically the barrier between the GI tract and the blood vessels and the drug will essentially then pass through the liver and be metabolized and then it ends up in the blood circulation. And when the drug ends up in the blood circulation, it's available to get to its target sites to

achieve its therapeutic effect. We measure that as the oral bioavailability.

Q. What are the reasons that Exelixis considered bioavailability in identifying the right salt?

A. Well, it was extremely important because we were developing cabozantinib as an oral administration drug. So, it was critical that cabozantinib have higher bioavailability in the high blood -- high drug concentration in the blood levels.

Q. What factors affect the oral bioavailability of cabozantinib?

A. So, cabozantinib in particular, was quite unique with respect to its features that resulted in high bioavailability. Cabozantinib was seen to have a high permeability, which is essentially its ability to pass through that epithelial wall.

It also was seen to have a long half-life. And, you know, most drugs can have half-lives of around, you know, 10 to 12 of hours. Cabozantinib had a half-life of around 96 hours, which meant that it would stay in the blood circulation for almost four days, which was also extremely important because it would then continue to achieve its bioavailability.

An then lastly, but also importantly, cabozantinib when metabolized by the liver actually had an

active metabolite, which again meant that once the active metabolite was circulating in the blood circulation, it was continuing to help achieve a therapeutic effect.

So those are the three things that were particularly important for cabozantinib.

Q. You mentioned permeability. What is that?

A. Yeah. So permeability is -- is the ability of a compound to essentially travel from the GI tract through the epithelial wall into the blood stream. And in this particular case, cabozantinib demonstrated a high permeability based on the data that was generated.

Q. What role does permeability play in the oral bioavailability of cabozantinib?

A. It's extremely important because as we discussed since the tablet or capsule has to release the drug and the drug has to pass through the epithelial wall, if it were not for the high bioavailability of cabozantinib, you would not get as much drug across the wall and into the blood circulation. So it was extremely important.

Q. What role does dissolution play in the oral bioavailability of cabozantinib?

A. Dissolution was extremely important because, again, we're dealing with cabozantinib, which was an oral -- oral drug and it was extremely important that the tablet or capsule dissolve and disintegrate immediately so that the

contents of the tablet/capsule would be released into the bloodstream, therefore available for obviously the activation.

Q. What role does solubility play in the oral bioavailability of cabozantinib?

A. So, while solubility was a factor for cabozantinib development, really what the -- what was more of a key driver was the high bioavailability of cabozantinib combined with the, you know, excellent solid state properties.

Q. So how did all of these properties that we've been discussing influence salt selection for cabozantinib?

A. Right. So really based on that -- based on all the work that was done, all the properties are evaluated, the key driver was really the fact that we were seeing great oral bioavailability from the (L)-malate salt and that was one of the key drivers for selecting the malate salt.

MR. PRUSSIA: If we could have PTX-94. It's Tab 4 in your binder if you need it.

BY MR. PRUSSIA:

Q. What is this document?

A. This is what we call the technical evidence candidate selection document for cabozantinib.

Q. Is this an Exelixis document?

A. Yes.

Q. Is it the type of document that the company creates

in the ordinary course of its business?
A. Yes, it is.
Q. What is a technical evidence candidate selection report?
A. Right. So at a high level, it essentially summarizes the, obviously, enormous work that's generated when taking a compound from the discovery phase through the evaluation phase, as the medical chemists do, in order to get to the point where a compound is ready to be nominated to proceed through the -- to the development phase.
And some of the key highlights in the document are biochemical assays, cell assays, the results are a considerable amount of what we call PKPD, pharmacokinetic—pharmacodynamic data. And it also include things like tumor regression analysis showing that tumors are shrinking when the drug is delivered and also a considerable amount of in vivo data as well.
Q. There's a reference to EXEL-02977184. What does that refer to?
A. Yeah, so that's just an old code for cabozantinib.
Q. Now, what salts had Pharmorphix identified for further consideration for Exelixis' use?
A. Right. So there were five salts evaluated and recommended for further evaluation by Pharmorphix. There were obviously the (L)-malate salts, hydrochloride salts,

phosphate salts, maleate salts, not to be confused with the malate salt, and (L)-tartaric salts.

Q. By when did Exelixis ultimately select the malate salt for further development?

A. You know, it was around the time of this report and that kind of middle of 2004.

Q. What solid form did the company select for commercial manufacturing?

A. That would be the (L)-malate crystalline salts.

Q. Did you submit a declaration during the prosecution of the crystalline malate salt patents?

A. Yes.

MR. PRUSSIA: Let's please bring up PTX-225.

BY MR. PRUSSIA:

Q. What is this document?

A. So this is the declaration that was submitted, as you mentioned.

MR. PRUSSIA: And if we turn to Figure 2.

BY MR. PRUSSIA:

Q. Generally, what information did you provide to the Patent Office in your declaration?

A. Yeah. So at a high level, the data included in this document was summarizing the effect of studying the dissolution of the (L)-malate crystalline salts in tablets or capsules, as compared with adding amorphous malate salt

to those tablets and capsules and then assessing the performance of the dissolution. And this graph is an illustration of that.

Q. What does the top line reflect?

A. So the top line reflects when the capsule in this particular case was produced using the 100 percent crystalline malate salt material.

Q. And what does the bottom line reflect?

A. So in the bottom line, the capsule had 20 percent of the amorphous salt added to it. And as you can see, there was a significant difference in the profiles.

Q. And what were the results of the dissolution experiments?

A. Yeah. So the results were particularly surprising in that the crystalline -- 100 percent crystalline material dissolves extremely fast, rapidly compared with the capsules that were spiked with the amorphous material.

Q. What are the reasons that you found this surprising?

A. So it was particularly surprising because, generally speaking, amorphous compounds and materials dissolve faster than the crystalline material. So in this case, having formulated 100 percent crystalline material compared with the amorphous and seeing such a difference in dissolution was -- was very surprising.

Q. What is the impact of the rapid dissolution of the

crystalline malate salt on the oral bioavailability of Cabometyx and Cometriq?
A. Yeah. Extremely important because, again, we're developing an oral, bioavailable drugs and ensuring that the tablet or capsule was dissolving as quickly as possible was fundamentally important.
Q. What did the Patent Office do in response to the evidence presented in your declaration?
A. They accepted the claims.
MR. PRUSSIA: If we can pull that down.
BY MR. PRUSSIA:
Q. I'd like to shift gears and talk about another topic.
What were -- manufacturing in particular.
What were some of the challenges Exelixis faced during the manufacturing of Cabometyx and Cometriq?
A. Yeah, significant challenges. You know, Exelixis was taking med chem -- a chemistry process and scaling it up, developing it over a number of years in order to scale it, in order to produce suitable API for use in the clinic.
There were many experiments that were performed on the chemistry side of things to get the active ingredient to the point where it had been optimized and the process was acting robustly and consistently, and then the tablets formulation work was also particularly important in order to get -- to produce, you know, tablets that optimize the

tablet manufacturing process and gets the tablets to produce, you know, consistent product.

And in particular, I would say there was obviously lots of -- lots of areas that had to be optimized for the API and the product, particularly for the API, there was an impurity, the 6,7-dimethoxy-quinoline-4-ol, and that was particular challenge, certainly from the API standpoint.

Q. What challenges were presented -- presented in controlling the impurity profile of the API?

A. Right. So in particular with this 1-1 impurity, because it was a starting material in the API synthetic process and an impurity but also a degradant, it was particularly challenging because the degradant would form during the subsequent manufacturing steps of the API, therefore particularly challenging to control.

Q. Now, can we refer to the 6,7-dimethoxy-quinoline-4-ol impurity as the 1-1?

A. Yes.

Q. Okay. What is the significance that 1-1 appears as both starting material and as a degradant?

A. Well, particularly challenging because, you know, if it was just a starting material, you would expect that with subsequent chemistry steps. You would be able to purge that material and essentially eliminate it prior to the completion of the manufacturing process, but in this

particular case, because the 1-1 was a degradant, it was basically decomposing from the subsequent chemistry steps. And as it was decomposing, it was showing itself up in the finished API and, therefore, quite challenging to control.

Q. How did Exelixis discover the 1-1 impurity?

A. Right. So Exelixis, initially there was a in silico screen that was conducted where all the different potential impurities and actual impurities of the API were examined through the in silico process which is a computational process that provides structural alerts for impurities, and the 1-1 impurity was found to be positive in that particular evaluation. And then the unequivocal confirmation that the 1-1 impurity was indeed positive for genotoxicity was through what's called an Ames assay or a bacterial assay, which essentially confirmed that the 1-1 was indeed a genotoxic impurity.

Q. What is a genotoxic impurity?

A. So at a high level, a genotoxic impurity is essentially a compound that could damage DNA and potentially cause cancer in humans.

Q. Please mark PTX-35 on the screen.

It's Tab 6 of your binder. What is this document?

A. This is the manufacturing process development section of the NDA that was submitted to the FDA.

Q. And if I could direct your attention to Table 2, which is on the last page of the exhibit, at a high level, what is shown on Table 2?

A. Yeah, so at a very high level, Table 2 is essentially showing the evolution of the chemistry process from the initial scale-up of the med chem route to what's called process A1 in this table, and over years of work, the evolution of the process from A-1 to A-2 where, obviously, lots of optimization experiments that were performed. And then the process was optimized to what was called process B-1 with, again, considerable experiments were performed.

And then, finally, the process continued to be optimized in order to produce what we refer to as process B-2. That was considered to be the acceptable process that we commercialized eventually.

Q. In the fourth column there's a reference to Exelixis 184-1-1.

What does that refer to?

A. Yes, so as we've discussed, that the 1-1 is a genotoxic impurity that we were just discussing.

Q. There's a reference to PPM in that column.

What does PPM refer to?

A. Yeah, so PPM is essentially parts per million. It's a very -- I would say it's a very small, low number in detection.

Q. Are the ranges of 1-1 levels reported here in this table, are they for the API or for the formulated drug product?
A. The levels here are for the API only.
Q. Focusing on process A-2, that row there, what did Exelixis tell the FDA regarding the presence of the 1-1 impurity in API batches made using process A-2?
A. Yeah, so as we can see from this table, the amount of 1-1 that was produced from process A-2 varied from around 35 PPM to about 411 PPM. So, you know, Exelixis considered that to be quite variable and inconsistent relative to the 1-1 that was being produced from that process.
Q. Who made the API batches using process A-2?
A. So there was two contract manufacturers that Exelixis had contracted out to and in those times. One was called Regis, and one was a company called Girindus.
Q. What conclusions did Exelixis reach regarding the 1-1 levels produced by process A-2?
A. Yeah, so Exelixis' conclusion was that the process A-2 was inconsistent relative to the amount of 1-1 that was being produced and that the levels report as shown here, 35 to 411 PPM were unacceptable from a -- from a from a 1-1 standpoint in particular.
Q. Now, just focusing on that 35 PPM number, what are the reasons that it would not have been sufficient for the

company to move forward with a process that generates 35 PPM of 1-1 at the lowest level?

A. Yeah, for a few reasons. I mean, Number 1, as we discussed, the 1-1 was a genotoxic impurity. So as a genotoxic impurity, the 1-1 could potentially cause cancer to humans. So, we considered it extremely important to try to minimize the levels of the 1-1 to the lowest levels that we possibly could get to.

And secondly and importantly, the API, the active ingredient has to be formulated into a product, in this particular case, the capsule or the tablet. And there was a manufacturing process in the drug product and there's a formulation.

So, ultimately, patients take the product. So it's critically important for us to ensure that we have the lowest levels of the 1-1 impurity possible in the active ingredient knowing that there was going to be a likelihood of the 1-1 increasing in the drug product because we knew that the 1-1 increase in the presence of moisture, heat, and oxygen in particular.

Q. Just on that point, why would 1-1 levels be higher in the final drug product?

A. Well, our concern was that because the 1-1 was a degradant, and as a degradant, the 1-1 was seen to, with all the experiments that had been performed, increase in the

presence of heat, moisture, and oxygen. And the drug product manufacturing process has all those things at different steps, and so there was ample opportunities for the 1-1 to increase during the manufacturing of the drug product. So, that was why we particularly considered the numbers here to be, you know, too high.

Q. Now, focusing on B-2 now, what did Exelixis tell the FDA regarding the presence of 1-1 in API batches made with process B-2?

A. Right. So as we can see here, you know, with the sufficient -- with a significant amount of development and process optimization work, that was carried out between process A-2 all the way through process B-2. And Exelixis found that the levels of 1-1 were very low. They were in the range of, you know, less than 2 PPM to 12 PPM. So we felt -- Exelixis felt that this was a process by which we were producing the lowest levels of the 1-1 impurity that we possibly could.

Q. So, what are the reasons that the company needed to control the presence of the 1-1 all the way down to the 2 PPM level?

A. Yeah, again, it was extremely important to ensure that we had the lowest levels possible in the API because the API was going to be formulated into a drug product. It was going to be exposed to all the conditions that, you

know, we knew could cause a 1-1 to form. And, of course, the drug product needed to be able to be stable as well. So, it was extremely important to have at the lowest levels of 1-1 possible because, again, the 1-1 was a genotoxic impurity that could cause cancer to patients.

Q. Let's move to DTX-291. It's Tab 7 in your binder.
What is this document?

A. This is an international publication WO 2010/083414.

Q. Who is the first applicant?

A. Exelixis.

Q. What's the last name of the first listed inventor?

A. Brown.

Q. And if we -- if I could direct your attention to property example Number 1, what process is described here?

A. This is the process A-2.

Q. You can put that down and move to PTX-47. It's Tab 8 in your binder.
What is this document?

A. Yeah. So this is a section of the NDA titled components of the drug product which was submitted to the FDA.

Q. If we turn to Table 4, which is on Page 18.
What is the title of Table 4?

A. Yeah. This is an excipient compatibility study.

Q. And what conditions did Exelixis use for this study?

A. So Exelixis used conditions of 40-75, accelerated conditions, so higher temperature and humidity as well as dry and wet.

Q. What are the reasons that Exelixis selected these conditions?

A. All right. So since we knew that the 1-1 impurity was -- you know, was seen to increase through moisture, heat, and oxygen, it was particularly important for us to study the effect of the excipients on its active ingredient, monitor the levels of 1-1 in the conditions of, you know, high temperature, as well as water so we could understand how the 1-1 would behave.

Q. What process was used to make the API that was used in these studies?

A. That would be the final process, the commercial process B-2.

Q. Generally what happened to the levels of 1-1 for each excipient in this study?

A. Yeah, so generally as you can see, from the table, pretty much with most of the excipient combinations we saw an increase in the 1-1. But I'll point out importantly the starting point for the -- for the 1-1 was low, which was -- which was something that we found to be extremely important, given that most of these excipients could give rise to the 1-1.

02:44:19 Q. So what conclusions did the company reach regarding 1-1 formation during drug product manufacturing?
02:44:25 A. Yeah, so, again, it reinforced why it was extremely important to have the lowest levels of the 1-1 possible in the API given that, you know, these excipients combinations and in the presence of moisture, heat and oxygen, which these conditions were representing, that the 1-1 would likely increase in the presence of those -- you know, of those conditions. So, it was a -- it was extremely important information.
02:44:56 Q. Let's pull that down and move to JTX-4. It's Tab 9 in your binder.
02:45:02 Dr. Shah, what is this document?
02:45:04 A. This is a patent 11,298,349.
02:45:08 Q. Are you an inventor on this patent?
02:45:10 A. Yes.
02:45:12 Q. What was your role in the '349 patent invention?
02:45:15 A. Yeah, so my role was overseeing the drug product activities specifically.
02:45:21 Q. Who is Jo Ann Wilson?
02:45:23 A. So Jo Ann Wilson is a former Exelixis employee who oversaw the CMC development activities.
02:45:29 Q. Now, what synthetic process is disclosed in this patent?
02:45:32 A. This was the commercial B-2 process.

Q. And if we turn to Claim 3, do you see the reference to one or more fillers, one or more disintegrants, one or more glidants and one or more lubricants? Do you see that?
A. Yes.
Q. Does Cabometyx include one or more fillers, one or more disintegrants, one or more glidants and one or more lubricants?
A. Yes, it does.
Q. And what are the reasons that Exelixis uses a glidant in its formulation for Cabometyx?
A. Well, the glidant was extremely important because cabozantinib is a poor flowing API, and a glidant is designed to improve flow. Therefore, it was necessary for the formulation.
Q. And what type of granulation process does Exelixis use to manufacture the Cabometyx tablets?
A. That's a wet granulation process.
Q. Does Exelixis add the glidant before or after the wet granulation?
A. So Exelixis adds the glidant after the wet granulation.
Q. And what are the reasons that Exelixis adds the glidant after the wet granulation?
A. Well, it's extremely important because the glidant is supposed to enhance the flow properties. And when you --

when you perform the wet granulation, and produce the granules themselves, the granules are then mixed with what's called the extragranular blend, which includes an disintegrant.

And in order to have the granules and that -- that excipient material flow consistently, and particularly not segregated in that particular powder blend, the glidant is added because a glidant is intended to help with the flow of that material. So it's particularly important.

Q. Now, what step in the manufacturing process does Exelixis add its glidant?

A. So that would be the step right before we added lubricant.

Q. And what are the reasons that Exelixis adds the glidant at that step?

A. Well, the reasons why the glidant is added there is to help with the flow of the actual wet granulation, along with the extragranular excipients, right before the lubricant is added, because the glidant is supposed to help with the flow of the powder between the granules and the excipients that are in the powder blend. And the lubricant is intended to help the powder with respect to sticking on the tablet surface.

Q. Did you submit a declaration during prosecution of this patent?

A. Yes.

MR. PRUSSIA: If we could pull this down and pull up JTX-8 A.

BY MR. PRUSSIA:

Q. Which is Tab 10 in your binder.

What is this document?

A. So this is the declaration you referenced.

Q. And if we could focus on paragraphs 9 through 12. At a high level, what does this declaration describe?

A. So at a high level, the declaration contains stability data that Exelixis had generated -- that we had generated which showed the behavior of the 1-1 upon stability in the tablets and in the capsules.

Q. And what process was used to manufacture the API in the batches that are reported in your declaration?

A. The commercial process B-2.

Q. And what are the reasons that Exelixis conducted the experiments that are described in your declaration?

A. Well, it was extremely important because, again, as we're dealing with the 1-1, we wanted to ensure that we had the minimum amounts possible, so we needed to study how the 1-1 would behave on stability in both products.

MR. PRUSSIA: If we go to the table at Page 6 in the document.

BY MR. PRUSSIA:

Q. What were the results of the stability testing?

A. Yeah, so the results were interesting and surprising. You know, we saw growth of the 1-1 levels in the drug product, in the capsules. And not as much as we thought that we would see, given the 1-1, you know, was seen to increase in the presence of moisture, heat, and oxygen. But, again, we were starting at the very low levels of 1-1 in the API.

So, you know, we were -- ultimately we were -- we were satisfied that in the drug product we were able to maintain, you know, low levels of the 1-1.

Q. So what did these results tell you about the significance of process B-2?

A. Well, process B-2 was really the only way that we were able to keep the 1-1 levels consistently -- consistently low in the API, which enabled us to have essentially a product that was able to minimize and keep the 1-1 levels as low as we possibly could.

Q. Now, did Exelixis submit tablet and capsule stability data to the FDA?

A. Yes.

MR. PRUSSIA: If we could pull this down and pull up PTX-19.

BY MR. PRUSSIA:

Q. It's Tab 11 in your binder.

02:50:14 What is this document?
02:50:15 A. So this is another section of the NDA titled "Stability" that was submitted to the FDA.
02:50:22 Q. And which drug product is the subject of this submission?
02:50:26 A. This is the Cometriq capsule.
02:50:31 MR. PRUSSIA: And if we go to PTX-43.
02:50:31 BY MR. PRUSSIA:
02:50:35 Q. It's Tab 12 in your binder.
02:50:36 What is this document?
02:50:37 A. This is a stability section for the Cabometyx tablets that were submitted to the FDA.
02:50:45 MR. PRUSSIA: And if you go to PTX-29.
02:50:48 BY MR. PRUSSIA:
02:50:48 Q. What is this document?
02:50:49 A. This is a section of the NDA called "justification of specifications" for the capsule that was submitted to the FDA.
02:50:57 MR. PRUSSIA: And if we turn to Figure 3 at Page 8.
02:50:59 BY MR. PRUSSIA:
02:51:00 Q. What is shown at Figure 3?
02:51:01 A. Right. So, at a high level, the graph is showing us what we call linear regression. And what it's essentially showing is when you have a particular amount of 1-1 in the

API to start with, which essentially is -- if we look on the left-hand side of the graph, the Y axis is 1-1. And if you look at the low -- the left bottom of the graph, we can see that when we start off with a 1-1 level of around -- you know, around 5 PPM, as you -- as you -- as you go over time, all the way to 36 months, which is, getting to the right of the graph, you can see that there are results at 1-1 level in the capsules is at 29 PPM.

And as you go up the graph, where now the GTI 1-1 is 19 PPM, that then results in 1-1 after 36 months of 44 PPM. So we can see the 1-1 level increasing over time consistently all the way through to 36 months.

Q. And what process was used to develop the API that's used in this analysis?

A. This was the commercial process B-2.

Q. Now, what conclusions did Exelixis reach regarding this analysis?

A. Well, the conclusions were consistent in that it was, again, extremely important to have the lowest levels of the 1-1 possible. Because, as we can see, the 1-1 was increasing in the product. Therefore, we wanted to minimize that. And it was important to have the -- again, the lowest levels possible in the active ingredient.

Q. What conclusions did Exelixis reach regarding the ability of process A-2 to consistently and reliably meet

release specifications regarding 1-1?
A. Yeah, so we didn't think that process A-2 was acceptable. The range of 1-1, 35 PPM to 411 PPM, was inconsistent and variable. We weren't comfortable that that was -- that that was the lowest level of 1-1 that we could -- we could produce. So it was really important for us to continue until we had the commercial B-2 process that minimized those levels.
Q. Has the company conducted any experiments to demonstrate the robustness of process B-2?
A. Yes. Many experiments.
Q. Just generally what types of experiments?
A. Yeah, so, you know, we did hundreds of experiments. And Exelixis did hundreds of experiments looking at, you know, every step of the synthetic scheme, including things like varying heats, varying water, varying order of addition, varying solvent conditions.

There were multiple experiments to identify and optimize every single step in order to apply the right controls. One experiment in particular, that I recall, was the -- you know, what Exelixis had done was, at the first step of the synthetic process, to demonstrate that knowing that the 1-1 was going to degrade during the manufacturing process, Exelixis had taken 50,000 PPMs of the 1-1 and added it to the very start of the reaction. And subsequently

proceeded with the reaction. And this was obviously with the final commercial process B-2.

And Exelixis saw that, even with adding 50,000 PPM to the beginning of that reaction, with the finished API, there was non -- there was non-detected amount of 1-1. So I think it's just one example of many that demonstrated that really B-2, the process B-2 was a consistent reproducible manufacturing process that had all the controls in it, in order for it to be a suitable process for commercializing and obviously providing to cancer patient.

Q. Roughly, how many commercial batches of Cometriq and Cabometyx have been generated using process B-2?

A. Since we had approval for process B-2, we've made around 180 -- 180, 190 commercial batches.

Q. And roughly how many tablets and capsules does that translate to?

A. It translated roughly to around 50 -- I think 50 million tablets and millions of capsules.

Q. What were the levels of 1-1 in those batches, at a high level?

A. That's easy to answer. Every single batch had the -- met the specification. Every batch had the extreme low levels of 1-1. Every capsule, every tablet, every API batch.

Q. And just to -- just remind us, how many batches of

process A-2 have been created?

A. In total, I believe there were four.

Q. Now, what role does process B-2 play in the commercialization of Cometriq and Cabometyx?

A. It's extremely important. Had we not -- if we were not able to develop process B-2, develop the chemistry, optimize the process, put the necessary controls in place, and in particular to minimize the 1-1, you know, we would not have been able to develop a product that essentially was able to keep the 1-1 levels as low as possible.

And it was extremely important for us because the 1-1 was a genotoxic impurity and, you know, our trials are for patients with cancer. So we wanted to make sure that the 1-1 was at the lowest levels possible.

Q. Just a few more questions.

Since you are involved in the submission of documents to the FDA, we looked at several documents today that the company submitted to the FDA; right?

A. Yes.

Q. And what is the process for preparing and reviewing these documents before they are submitted to the FDA?

A. Yeah, so, the process is extremely vigorous. First of all, we start with the data being provided from the contract manufacturer, who, you know, manufactures the product. And that data is scrutinized line by line. Every

line of the batch record, every piece of raw data is analyzed and looked at by the technical experts within Exelixis, the S subject matter experts, so to speak.

We have a quality assurance team that reviews data very carefully and meticulously, compares it to the source data to make sure that it's accurate and correct. We have a regulatory team within Exelixis that then reviews the entire submissions, again, very meticulously.

And then finally we have a formal company, you know, leadership sign off on documents before they're submitted to regulatory agencies.

MR. PRUSSIA: That you, Dr. Shah.

I have no further questions, Your Honor. May I move the exhibits now.

THE COURT: Sure.

MR. PRUSSIA: Exelixis moves PTX-4, PTX-1, PTX-94, 225, 47, 19, 43, 29, and JTX-8 A.

MR. COOPER: No objection.

MR. MATHAS: No objections, Your Honor.

THE COURT: Admitted without objections.

(PTX Exhibit Nos. 4, 1, 94, 225, 47, 19, 43, 29 were admitted into evidence.)

(JTX Exhibit No. 8 A was admitted into evidence.)

THE COURT: Cross.

MR. MATHAS: Thank you, Your Honor. May I hand up come cross binders.

THE COURT: Sure.

THE WITNESS: Thank you.

CROSS-EXAMINATION

BY MR. MATHAS:

Q. Good afternoon, Dr. Shah.

A. Good afternoon.

Q. Let's start talking with -- talking about salt screening. Now, salt screening is performed to identify pharmaceutically developable -- a pharmaceutically developable salt of a compound; is that right?

A. Yes. That's correct.

Q. And one of the reasons for running a salt screen is to try to find a salt that increases the solubility as compared to the free base of a compound; right?

A. I'd say that's a general assumption. I suppose it depends what the purpose of the salt screen is for and the nature of the particular compound.

Q. It is certainly one of the factors that can be a reason for running a salt screen; right?

A. Sure.

Q. All right. Now, in 2004, I think you told us that Exelixis hired a company called Pharmorphix to run a salt screen on the cabozantinib free base; is that right?

A. Yes.
Q. And Pharmorphix had expertise in running salt screens; true?
A. I believe so. Yes.
Q. All right. And Exelixis provided Pharmorphix with a cabozantinib free base; right?
A. Yes.
Q. And Pharmorphix was charged with conducting the salt screen on Exelixis' behalf; right?
A. That's my understanding, yes.
Q. Okay. And there was nothing unique about the cabozantinib molecule that would make a salt screen of cabozantinib free base complex; isn't that right?
A. I'd say based on my experience, salt screens are always complex. There's nothing really straightforward about them because there's a lot of trial and error in art and, you know, significant science involved in salt screening.
Q. I don't think that was my question, Dr. Shah.
Is there -- it's true, isn't it, that there was nothing about the cabozantinib molecule that made running a salt screen on it complex?
That's true; isn't it?
A. I suppose I couldn't say that because Pharmorphix, you know, were the experts who performed the salt screen, so

they applied their expertise at the time.

MR. MATHAS: Okay. Let's look at your deposition; this is your 2021 deposition. And we'll call up page 141, starting at Line 22.

And you were asked here: "So you said Pharmorphix is capable of performing complex experiments, I think were your words. Is there anything about the cabozantinib molecule that made these experiments complex?"

And then your answer there, sir, was: "I can't think of anything specifically."

BY MR. MATHAS:

Q. Is that right?

A. Yes.

Q. And were you asked that question and did you give that answer?

A. Yes. Looks like I did, yes.

Q. All right. So let's look at that Pharmorphix report that you alluded to but didn't show us during your direct.

MR. MATHAS: And for that, let's pull up PTX-87.

BY MR. MATHAS:

Q. And this is the report that came out of the work that -- excuse me -- Pharmorphix did on behalf of Exelixis; right?

A. Sorry. Just give me one second.

Q. Sure. It will be on the screen. If you want the

hard copy, that's fine too. Whichever is better for you.

Dr. Shah, you recognize this document, PTX-87, as the report that Pharmorphix presented to Exelixis; right?

A. Yes.

MR. MATHAS: All right. And I want to take a look at the third page of the document, about halfway down there. There's a paragraph starting "A suitable" -- let's pull that up.

BY MR. MATHAS:

Q. All right. And so Pharmorphix reports that "a suitable acid screening set consisting of 22 acids was selected." I'm going to stop there.

Do you see that?

A. Yes.

Q. And so what Pharmorphix did was they selected 22 suitable acids to include in their salt screen; right?

A. That's my understanding.

Q. Okay. And -- and the way that they selected those acids was based on a measure of pK_a and Tong and Whitesell Rule-of-2 guideline; isn't that true?

A. That's what is written, yes.

Q. And that's how they did it; right?

A. Well, I mean I can't speak to exactly what the Pharmorphix scientists used. Certainly the Tong rule was a guideline that existed. I'm sure that was referenced as --

as we can see here.

Q. Well, Pharmorphix told Exelixis that that's what they did; right?

A. Sure. It's referenced here. Yes.

Q. And you're not aware of any evidence in your history with the company that somehow this wasn't what Pharmorphix did. Are you, sir?

A. I am not.

Q. All right. Now, and you, yourself, you were aware of Tong's Rule-of-2 as of the mid-2000s as a person working in this field; right?

A. Yes. I was aware.

Q. Okay. And Tong -- the Tong paper -- there's a Tong paper that refers to this Rule-of-2; right?

A. Yes.

Q. Okay. And it is referred to by the Pharmorphix folks as the Rule-of-2 in this document as well; right?

A. Correct. Yes.

Q. Now, in conducting their salt screen that Exelixis hired Pharmorphix to run, Pharmorphix did not use any Rule-of-3, did they?

A. I'm not aware of -- of whether they did or did not.

Q. Right. You're not aware of any evidence that in conducting this salt screen they used the Rule-of-3; isn't that true?

A. I'm not aware. I mean I guess the only thing I could say contextually is they -- they performed a salt screen with different counterions and I don't think all of them worked per se with the Rule-of-2. So, that's -- that's about all I know relevant to what was produced.

Q. Very simple question, Dr. Shah. You have no evidence that Pharmorphix used a Rule-of-3 in selecting its counterions; right?

A. No, I do not.

Q. All right. And the evidence that we've seen shows they used the Rule-of-2; isn't that right?

A. According to what's written here.

Q. All right. And malic acid was one of the 22 suitable salts that Pharmorphix selected for inclusion in salt screen based on Tong's Rule-of-2; right?

A. Yes.

Q. All right. Now, originally in the development --

MR. MATHAS: And you can take that down.

BY MR. MATHAS:

Q. In the development of cabozantinib, Dr. Shah, Exelixis believed that cabozantinib (L)-malate existed in only one polymorphic form; right?

A. That's correct.

Q. And in 2010, Exelixis' development partner, Bristol Myers Squibb, identified two separate forms of cabozantinib;

right?
A. Closely related, yes, two forms.
Q. Two forms, N-1 and N-2; true?
A. Yes.
Q. All right. And BMS characterized the forms to show that N-1 and N-2 were two different polymorphs; right?
A. Yes, that's right. BMS showed that they were two polymorphs, the N-1 and the N-2.
Q. Right. And so it was BMS -- excuse me -- BMS scientists that first identified the existence of form N-1 and N-2; right?
A. Yes.
Q. And form N-1 and N-2 are obviously different forms; right?
A. N-1 and N-2 are closely related, but they are two distinct polymorphs.
Q. Right. They're similar, but obviously different; right?
A. Yes. They're two -- they are two different polymorphs.
Q. But they're obviously different; right?
A. Sorry. Could you -- could you clarify your question? What do you mean by "obviously different"?
Q. Well, let me ask you this: In order to determine that they were different forms, BMS conducted

characterization tests on form N-1 and N-2 right?
A. That's my recollection, yes.
Q. Okay. And what characterization tests did BMS perform?
A. Well, it's been a while since I've seen the report, but I know they -- they conducted multiple solid state evaluations. If memory serves, they performed DSC, TGA, obviously XRPD, MMR. There was a plethora of experiments that I believe that they performed.
Q. All right. And those are standard ways to characterize different polymorphs; aren't they?
A. Well, there are certainly different techniques that can be used to characterize different polymorphs. Yeah.
Q. And different polymorphs will have different characteristics; true?
A. Are you asking me generally?
Q. Yeah.
A. Generally speaking, yes. Different polymorphs can have different characteristics.
Q. Right. And different polymorphs can have different properties; right?
A. Yes. I'd say different polymorphs can have different properties.
Q. All right. And some polymorphs may have more favorable properties for drug development than other

polymorphs; right?
A. In a general sense.
Q. Yeah. And in drug development, companies choose whether to develop a polymorph based on the polymorph's characteristics; right?
A. Well, again, I suppose it depends on what they -- the development goals are relative to the compound.
Q. Sure. For example, one compound or one polymorph might be more stable than another polymorph, which causes a company to choose the more stable form.
That can happen; can't it?
A. Yes. Certainly they would not want to move an unstable form forward.
Q. All right. And so as of 2015, the only polymorphic forms of cabozantinib that Exelixis was aware of were the N-1 and N-2 forms; right?
A. I believe so. Yes.
Q. Okay. And you're familiar with FDA guidance documents, Dr. Shah; right?
A. Oh, yes. Yeah.
Q. And you review them and you use them in your line of work and you follow them and Exelixis follows them when submitting things to the FDA; true?
A. We absolutely do, yes.
MR. MATHAS: Okay. Let's look at one of those

03:08:07 real quick, DTX-67.
03:08:07 BY MR. MATHAS:
03:08:16 Q. All right. And this is a -- you recognize this as a
03:08:19 FDA guidance document from 2004 Guidance For Industry?
03:08:23 A. Yes. Yes, I do.
03:08:25 MR. MATHAS: Okay. I want to go to Page 8 of
03:08:28 this document.
03:08:28 BY MR. MATHAS:
03:08:29 Q. And you're familiar with what this requires; right?
03:08:32 A. Yes. It's been awhile since I've looked at this.
03:08:35 But, yeah, I'm sure I was very familiar at the time.
03:08:37 Q. Sure. And one of the things that this document
03:08:39 requires is that -- that in submitting NDAs that -- that
03:08:43 companies like Exelixis have to identify the polymorphic
03:08:46 forms that they are aware of; right?
03:08:47 A. Yeah. The goal is to identify any polymorphs
03:08:51 relative to the active ingredient.
03:08:55 MR. MATHAS: All right. And if we look there in
03:08:56 the third line down, 3.2.S.3.1.
03:08:56 BY MR. MATHAS:
03:09:02 Q. Second sentence there it says, "The total number of
03:09:04 polymorphs should be listed here"; is that right?
03:09:07 A. That's what is stated here, yes.
03:09:09 Q. Okay. So the FDA tells companies like Exelixis to
03:09:11 tell us how many polymorphs you have; right?

03:09:14 A. Yeah, I'll add that there is actual a Q and A follow-up document to this document that specifically provides more specific guidance about what should be included and that document actually states the polymorphs that could be formed relative to the active ingredient only should be provided and other polymorphs should not be provided.

03:09:38 Q. All right. Well, in any event, Exelixis decided to tell the FDA what polymorphs it had identified and what it hadn't; right?

03:09:46 A. Exelixis provided the information for the N-2 and the N-1 polymorphs since that was relevant to the active ingredient, yes.

03:09:55 Q. Sure. And we can look at that.

03:09:57 MR. MATHAS: Let's go to DTX-20 at Page 2. And if we can see there, we'll just call out the first paragraph. I think we'll see what we need to see.

03:10:08 BY MR. MATHAS:

03:10:11 Q. There you were referring to Exelixis identified that cabozantinib was found to exist in two neat, closely related crystalline solid forms, N-1 and N-2; right?

03:10:21 A. That's correct. Yes.

03:10:22 Q. And so Exelixis followed the guidance and told FDA the forms that cabozantinib existed in; right?

03:10:29 A. That's correct, we followed the guidance. This is

what the -- this is the information we disclosed. We actually met at the FDA as well to discuss this data and what would be submitted to them.

Q. Okay. Now, if we look down a couple more lines we see there, there's a sentence that says "no other forms were identified in those studies."

Do you see that?

A. That's right.

Q. And that's information that FDA or that Exelixis told the FDA in their NDA as well; right?

A. Yes.

Q. Okay. Now, I want to talk for a minute about the --

MR. MATHAS: You can take that down.

BY MR. MATHAS:

Q. -- and talk about the malate salt patents. Now, you're not an inventor on the malate salt patents; right?

A. No.

Q. But you gave us some testimony today about how malic acid was chosen and things that were done about the malate salt patents; right?

A. Yes.

Q. Okay. And, in fact, during the course of the case, you were designated as Exelixis '30(b)(6) witness to testify as to certain topics of the malate salt patents; right?

A. I believe so. I'm not familiar with the number that

you mentioned specifically, but I would assume so, yes.
Q. Oh, I'm sorry, I'm sorry. But you gave a deposition. I got to ask you some questions about topics.
Do you recall that?
A. I do.
Q. And some of the topics related to the malate salt patents?
A. Yes.
Q. Okay. And one of the topics that I got to ask you questions about had to do with the crystalline forms that were disclosed in the specification of the malate salt patents other than N-1 and N-2.
Do you recall that?
A. Not specifically. But I'm -- if you say so, I'm sure it came up.
Q. Okay. All right. And I took your deposition and I asked you about the disclosure of the patent, and you and I looked at it. And I asked you -- if you could identify for me where in the malate salt patent it identified any form, polymorphic form, other than form N-1 and N-2.
Do you recall that?
A. I believe so. Yeah.
Q. Okay. All right. And I asked you and we went around and around. And I said, "Can you identify for me by name or number any form other than N-1 and N-2?"

Do you recall that?
A. I believe so.
Q. All right. And it's true, isn't it, that you in the deposition as Exelixis' 30(b)(6) witness, you were not able to identify for me by name or number any polymorphic form of cabozantinib in the malate salt patent specifications other than N-1 and N-2; that's true, isn't it?
MR. PRUSSIA: Your Honor, I object. There's no impeachment. He can't just read --
THE COURT: No, I don't think it is. It's not impeachment.
MR. PRUSSIA: He's reading the deposition. He's just -- he should just ask the question.
THE COURT: Yeah, in the ideal world, there wouldn't be all that lead-up. But we're not in the ideal world, so why don't we just answer the question and move on, if you remember the question.
THE WITNESS: Could you repeat the question.
BY MR. MATHAS:
Q. As -- when I asked you to identify by name or number any other polymorphic form other than N-1 or N-2 in the specification of the malate salt patents as Exelixis' 30(b)(6) witness, you didn't give -- you didn't identify any other polymorphic form by name or number; isn't that right?
A. Yes.

Q. All right. Let's talk for a minute about capsule development. Now, you joined Exelixis in mid-2009; true?
A. That's correct.
Q. And by then, Exelixis had already developed a cabozantinib (L)-malate capsule dosage form; right?
A. Yes.
Q. And by that time, in 2009, that capsule dosage form had already been used in clinical trials; true?
A. I believe the phase 1 study had already been started, yes.
Q. Right. And the phase 1 study included capsules that had API in them that had been manufactured by Regis who you talked about during your direct; right?
A. I believe so. Yes.
Q. Okay. And now, in addition to the cabozantinib (L)-malate in those clinical trial capsules, those capsules included a filler, a disintegrant, a lubricant, and a glidant; right?
A. You're asking me to recall what was in it because it's been awhile since I've looked at those documents. I assume so, yes.
Q. Well, if you need to refresh your recollection, I can do that. Do you know, sitting here, sir, whether or not the capsules in the clinical trials included a filler, a disintegrant, a lubricant and a glidant?

A. I believe so.
Q. Okay. All right.
Now, formulating an oral dosage form with a filler, a disintegrant, a lubricant and a glidant would have been well known as of 2009; isn't that true?
A. Are you asking me a general question?
Q. Yes.
A. I'd say it mostly depends upon the type of formulation that's being developed.
Q. Okay. But you -- you yourself, sir, as a person in this field, you were familiar with the use of those four excipients in formulations as of 2009, weren't you?
A. I was certainly aware of these different types of excipients, yes.
Q. All right. And, in fact, these four types of excipients, they were commonly used standard excipients; right?
A. Other specific excipients are you asking me about or just the general excipients.
Q. I'm talking about the four excipients that are in the claims that were in the capsules in the clinical studies. Those were commonly used standard excipients; right?
A. I guess, based on my experience, I would say, sure, people would have been aware that there are glidants, fillers, binders and lubricants.

03:16:13 Q. Well, let's look at what Exelixis told the FDA then.
03:16:16 MR. MATHAS: Pull up DTX-82.
03:16:18 THE COURT: Is this really in dispute?
03:16:19 MR. MATHAS: I hope not, Your Honor, but we
03:16:21 asked for a stipulation on it, and we're still here, so...
03:16:28 DTX-82 at 12, please.
03:16:28 BY MR. MATHAS:
03:16:33 Q. This is one of the NDA documents; right?
03:16:37 A. I believe so. Yes.
03:16:40 Q. All right. And Exelixis explained about the capsule
03:16:44 formulations, that they used standard excipients that
03:16:46 offered accepted functionality; right?
03:16:49 A. Correct.
03:16:55 Q. Now, there was nothing novel about using a filler, a
03:16:58 disintegrant, a lubricant and a glidant; right?
03:17:00 A. Sorry, I'm not sure what you mean by "novel."
03:17:04 Q. Well, it's true, isn't it, that Exelixis --
03:17:07 THE COURT: That sounds a lot like a question to
03:17:11 ask the expert. I understand that he's got expertise, but
03:17:13 he's not the expert. So why don't you save that for the
03:17:16 expert.
03:17:17 MR. MATHAS: Yes, Your Honor.
03:17:27 Let's look at a document you looked at during
03:17:30 your direct, PTX-35 at Page 16. And you can pull up this
03:17:41 table here.

BY MR. MATHAS:
Q. This is another table out of the NDA; right?
A. That's correct, yes.
Q. And you showed this table during your direct, and you focused on the column, the fourth column over on the contents of the 1-1 impurity in cabozantinib; right?
A. Yes.
Q. And specifically focusing in on the A-2 line, now, it's true, isn't it, Dr. Shah, that that A-2 line includes batches that were manufactured both by Regis and by Girindus?
A. Excuse me. That's correct, yes.
Q. Okay. And you did not in the course of your direct, present the Court with any underlying data from which these numbers were derived; true?
A. I don't believe we looked at any data, no.
Q. Okay. And, in fact, Exelixis doesn't even have the underlying data from which these numbers were derived; isn't that true?
A. I'm sorry. I'm not exactly sure what your question was.
Q. Well, you've -- you've not seen the underlying data that supports this 35 to 411; right?
A. I -- I'm -- no, I'm not as familiar with this source data.

03:18:53 Q. And you've not seen -- during your direct, you didn't present any data that showed testing on the Regis lots, the Regis A-2 lots that had a level of the 1-1 impurity over 200 PPMs; isn't that right?

03:19:09 A. Yeah, I mean, this is the table that we looked at.

03:19:12 Q. Okay. And this table includes both Regis and Girindus; true?

03:19:15 A. Yes.

03:19:16 Q. All right. Skip forward here. Let's talk -- you talked about two declarations during your direct, one that you submitted in connection with the malate salt patents, and I want to start there. So I think that was DDX-225.

03:19:45 MR. MATHAS: If we can pull that up.

03:19:50 I'm sorry. PTX-225.

03:19:50 BY MR. MATHAS:

03:19:54 Q. And, Dr. Shah, this was a declaration that you submitted in the malate salt prosecution?

03:19:59 A. Yes. That is right.

03:20:02 Q. And this had to did with some dissolution profiles between the amorphous and N-2; right?

03:20:07 A. Yes, that's right.

03:20:10 Q. Okay. And I think you said on direct that these results were particularly surprising; yeah?

03:20:16 A. Yes.

03:20:17 Q. Now, it's true that nowhere in this declaration that

you submitted to the Patent Office do you use the word "unexpected" or "surprising"; right?

A. I'd have to look at it to see whether that language was used or not.

Q. All right. Now, let me ask you this, the -- this document doesn't rule out that the dissolution of the amorphous was unexpectedly bad; right?

A. Sorry. I'm not exactly sure what you -- what your question is.

Q. Well, I think what you said on direct is that the dissolution of the N-2 was unexpectedly good; is that right?

A. Well, no, what I said was -- I believe what I said was the -- when comparing the dissolution.

Could we pull up the dissolution curve, if that's okay.

Q. Sure. If we go forward a page or two, probably. Is that what you were looking for?

THE COURT: I think once more.

THE WITNESS: Yeah, just go a little bit more.

BY MR. MATHAS:

Q. One more?

A. Yeah, okay. There you go.

Q. Okay. So --

A. Okay. So I believe what I recall that I said was in comparing the dissolution profiles that -- we actually

looked at the dissolution curve with capsules, but that's fine. Comparing the dissolution profiles, the drug products with the hundred percent crystalline material exhibited a much faster dissolution rate compared with the drug product that had the amorphous API added to it. And that was surprising in that the dissolution rate was faster with the hundred percent crystalline material.

Q. All right. Now, back in 2004, Exelixis conducted some dissolution studies comparing the amorphous contents versus crystalline cabozantinib; right?

A. Sorry, you lost me there. Did you say back in 2004?

Q. I'm sorry, 2014. And to do --

MR. MATHAS: Let's pull up PTX-161.

BY MR. MATHAS:

Q. PTX-161 is reporting on a amorphous XL184 is amorphous dissolution comparison.

Do you see that, Dr. Shah?

A. I see the title. I've not seen this document before, but I do see the title you're referring to.

Q. Okay. Now, one of the authors down there underneath it, it says, "K Shah." That's you; right?

A. I believe so, yes.

Q. Okay. And if we go forward to the fourth page of this document, what you found in this study comparing the amorphous in the crystalline forms was that "chunks of

undissolved material (gel-like lumps) were found in the amorphous material." Right?

A. Well, it's been a long time since I've seen this, but yeah that's what seems to be what was reported here.

Q. Okay. And if we go to Page 8 of the document.

A. By the way, is this in the binder?

Q. It is. It should be in your binder, yes.

A. Because by the way the binder just fell apart. It wasn't doing well. There's papers everywhere. So I'll do my best to keep up.

Q. I think this is the last page we're going to look at in this document, which is Page 8.

A. Okay. So if it's okay, if I need more, I may ask you to go up and down because I can't open the binder.

Q. Sure. And so there's a conclusion in this document. Do you see that there, Dr. Shah?

A. Sure.

Q. And the conclusion here was -- was that "amorphous material in contact with aqueous media tends to form gel-like lumps that do not disburse and are very slow to dissolve."

Is that right?

A. Are you asking me to confirm that -- the sentence at the bottom of the slide; right? That's what you just called out.

Q. That's the conclusion from this document; right?
A. Yeah, I mean, if I recollect -- I mean, this work was a very long time ago. The dissolution profiles were evaluated from the crystalline amorphous material. And yeah, I think these were the conclusions that the scientists had at the time.
Q. Okay.
MR. MATHAS: Let's turn and talk about your other declaration, which is JTX-8 A.
THE COURT: Before you do that.
Dr. Shah, the conclusions that were up there for 2014, or what they said about it, is that entirely consistent with what you said about it in your declaration that you submitted to the PTO?
THE WITNESS: Yeah. I think -- I think the reference on the slide that was just shown was -- at the bottom of the slide, was an inference back to the initial observations that BMS has had, whereby they saw slowing of the dissolution when they added small amounts of amorphous contents.
The declaration that we submitted was looking at that more extensively. So we had -- we had evaluated both the tablet formulation and the capsule formulation and added in 0 to 20 percent amorphous. So we could be really sure what the differences would be. And we included all of that

in the actual declaration itself.

THE COURT: All right. Thank you.

MR. MATHAS: All right. Let's go forward to JTX-8 A, please.

BY MR. MATHAS:

Q. Which is your other declaration that you showed. And I want to focus on paragraph 12, Dr. Shah.

A. Okay.

Q. All right. And in paragraph 12, you talk about the development of a storage-stable pharmaceutical composition; is that right?

A. Sure.

Q. And you say that "it was made difficult because exposure to water, atmospheric moisture or even residual moisture can cause degradation to form the 1-1 impurity"; true?

A. Yes.

Q. Okay. Now, in connection with this declaration, you did not submit any underlying data to support that proposition to the FDA; right?

A. Sorry, to the FDA?

Q. I'm sorry, to the PTO.

A. As part of the declaration?

Q. Correct.

A. Right. So the declaration -- again, I don't have the

entire document in front of me. But the declaration provides the stability data that was generated for tablets and capsules, and those data contain the 1-1, and showed the 1-1 change over time as part of the stability data. And that's what's in this declaration.

Q. Right. And I think, on your direct, you said that it was that -- it was surprising -- the stability data was surprising; is that right?

A. So I believe -- I believe what I said was through the extensive understanding that we had learned about the 1-1, and the fact that it was increasing in the presence of moisture, heat, and oxygen, we were surprised because once we had taken the -- again, this reminds me -- this was the commercial B-2 process.

Once we had taken the active ingredient, the API from commercial process B-2 at low levels, we were expecting to see a larger increase of the 1-1, because we were subjecting the 1-1 impurity -- we were subjecting the drug product to heat, moisture, and oxygen throughout the manufacturing processes. And then on stability as well.

So it was surprising that the levels of 1-1 were ratcheted up that high, as we had thought they couldn't be, based on all that knowledge.

Q. Okay. All right. So during your direct, you did use the term "surprising" in this context; right?

A. I -- yes, I did.
Q. Okay. And in your declaration, you don't use the word "surprising"; right?
A. Again, I -- I would have to read it to confirm it. So, I am not sure if that was used or not.
Q. Okay.
MR. MATHAS: Let's look real quick at PTX-29, Page 8, Figure 3.
BY MR. MATHAS:
Q. And this was the linear regression that you showed us. And just to make sure it's clear, this was a document that Exelixis used to determine if a particular material started at a particular PPM level, what would be expected to -- where would it be expected to be in 36 months; is that right?
A. Well, this document is what is characterized as a linear regression analysis. And, essentially, what it's showing is, if you start with the active ingredient at time 0 at a particular PPM, it shows the increase over that period of time, which you can see on the right-hand side. So it's showing you what you start with and then it's showing you up to what you can get to.
Q. Right. And -- and the way this works is the bottom line there is an actual result. And then the top line is a predicted result based on the slope; is that right?

A. Well, I suppose a couple of things. In the bottom line, as you can see, there are certain points on that line. That's where we had the actual data. So that line that you see at the bottom is projected out to the line -- the line on the right. So it's showing you what the potential detailed level would be in the line at the bottom.

And then essentially knowing that the rate of growth of the 1-1 would be fairly consistent with same formulation. We're now showing that if we increase the 1-1 level to 19 PPM, the resultant -- sorry, I'm pointing at my screen. Can't see my finger. But the resultant PPM would be 44 PPM, where the arrow is on that.

Q. Right. But the way that you got that was -- was using linear regression; right?

A. Yes.

Q. And linear regression uses the slope of the bottom line to plot the top line; correct?

A. That is correct.

Q. All right. That's all I wanted.

All right. Last topic. It's true, isn't it, Dr. Shah, that Exelixis did a significant amount of work on API synthesis in order to achieve a process for preparing API with low levels of the 1-1 impurity?

A. That's correct.

Q. Okay. And Dr. Wilson oversaw the API synthesis work;

true?
A. That's right.
Q. And through that synthetic chemistry process and process chemistry, Dr. Wilson and Exelixis were able to control for the 1-1 impurity in cabozantinib; right?
A. Yes.
Q. In the API; right?
A. Yes.
Q. Okay. And your role in the process then was to oversee drug product development; true?
A. Yeah, I saw also drug product development. I also participated in CMC meetings and interacted with Jo Ann Wilson, obviously, as part of the CMC team. And I oversaw the NDA submission for Cabometyx that included the API and, of course, the drug product as well.
Q. All right. And your formulation development team's job was to control the 1-1 impurity in the capsule and tablet dosage forms; right?
A. Well, my formulation team's job was to develop a formulation that had all the suitable characteristics that would be, you know, sufficient to have a formulation that would be suitable for commercialization at large scale.
Q. And part of that included ensuring that you minimized the genotoxic 1-1 impurity; right?
A. Well, certainly we -- we looked and monitored the 1-1

impurity after we had performed experiments in the tablets and the capsules.
Q. Yeah, part of -- part of your responsibility and your team's responsibility was ensuring that you minimized the genotoxic 1-1 impurity; true?
A. Well, we certainly didn't want to make it worse with the tablet or the capsule.
Q. Okay. Now, ultimately, you got -- you're a named inventor on the '349 patent; right?
A. I'm an inventor on the patent.
Q. Okay. And as part of that patent, it discloses information about how to synthesize the cabozantinib (L)-malate API to be free of the 1-1 impurity; right?
A. Yes.
Q. Okay. But the '349 patent does not require any specific way of formulating a tablet or capsule such that the tablet or capsule remains essentially free of the 1-1 impurity; right?
A. Yeah, I can't recall specifically what the language is in the patent, I'm not a patent expert. I mean, my job is to do the science and, you know, leave that job to our patent experts to put those -- information together.
Q. Sure. Well, let's -- let's look at it real quick.
MR. MATHAS: '349 patent, Column 21, Lines 37 to 45.

BY MR. MATHAS:

Q. And -- and this is -- this is from your '349 patent, Dr. Shah. And in the '349, you say that "tablet and capsule compositions can be prepared according to methods available to the skilled artisan"; is that right?

A. That's what's stated here.

Q. Okay.

MR. MATHAS: And if we go back to Column 20, Lines 38 to 49.

BY MR. MATHAS:

Q. You describe that "known techniques for the bulk preparation and production into unit dosage forms can be used to make composition of the invention"; right, Dr. Shah?

A. I think you read a line from that paragraph. Sorry.

Q. That's right. "Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein" and then it goes on; right?

A. That's what's written here, yes.

Q. Okay. And that's -- that's a true statement in your patent; right?

A. Yes, that's what's stated in the patent.

MR. MATHAS: All right. No further questions.

THE COURT: All right. Is there any redirect?

MR. MATHAS: Your Honor, before that, I'd move a couple of exhibits. PTX-87, DTX-67, DTX-20, DTX-82 -- I'm sorry -- yeah, DTX-82, and PTX-161.

MR. PRUSSIA: I have no objection.

THE COURT: All right. They're admitted without objection.

(PTX Exhibit Nos. 87 and 161 were admitted into evidence.)

(DTX Exhibit Nos. 67, 20, and 82 were admitted into evidence.)

REDIRECT EXAMINATION

BY MR. PRUSSIA:

Q. So, Dr. Shah, on this last point, what are the reasons why a pharmaceutical composition of cabozantinib (L)-malate, that only -- that does not -- that includes those excipients, generally, without identifying any specific type of excipient, what are the reasons that that pharmaceutical composition can be achieved and be essentially free of the 1-1 impurity?

A. Right. Well, as we discussed before, the only way that that could be achieved would be having the lowest levels of the 1-1 impurity possible in the active ingredients. Hence, the commercial process B-2.

Q. And what is -- sorry. You answered it.

MR. PRUSSIA: Okay. Nothing further, Your Honor.

THE COURT: All right. Dr. Shah, thank you. Watch your step stepping down. Okay.

All right. Well, we'll recess for 15 minutes. See you then.

DEPUTY CLERK: All rise.

(Recess was taken.)

DEPUTY CLERK: All rise.

THE COURT: All right. Let's continue.

MR. PRUSSIA: One quick housekeeping thing, Your Honor. The Pretrial Order required fact witnesses to be sequestered. Now that Dr. Shah has testified, MSN has consented for him to return to the courtroom. Thank you.

THE COURT: Okay.

Ms. Wigmore?

MS. WIGMORE: Your Honor, for our next witness Exelixis calls Dr. David MacMillan.

THE COURT: Okay.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: David MacMillan. D-A-V-I-D. W-I-L-L-I-A-M. C-R-O-S-S. M-A-C-M-I-L-L-A-N.

DAVID MacMILLAN, the witness herein, after having been duly affirmed under oath, was examined and

testified as follows:

THE WITNESS: I do.

MS. WIGMORE: May I proceed?

DIRECT EXAMINATION

BY MS. WIGMORE:

Q. Good afternoon, Dr. MacMillan. Would you please introduce yourself?

A. Yes. My name is David MacMillan.

Q. Have you been retained by an expert -- as an expert by Exelixis, Inc. in this case?

A. Yes, I have.

Q. Are you being compensated for the time you spend on the case?

A. Yes.

THE COURT: You know, that's not the correct second question. The correct second question is: Have you won any recent prizes you want to tell me about?

MS. WIGMORE: I was working up to that, Your Honor.

THE COURT: Sorry. I'm -- go ahead.

Well, so we were debating whether you wouldn't change your resume to put Nobel prize up a little higher on the first page, maybe even right underneath your name.

THE WITNESS: I was thinking about changing my daughter's middle name, but...

THE COURT: All right. I'm sorry. Go ahead.

BY MS. WIGMORE:

Q. Dr. MacMillan, does the compensation you are receiving have any influence of the opinions you're offering here?

A. No.

MS. WIGMORE: If we could please have PDX-2.

BY MS. WIGMORE:

Q. Where do you work, Dr. MacMillan?

A. I'm a professor of chemistry at Princeton University.

Q. And do you conduct research as part of your role at Princeton?

A. Yes, I do.

Q. Aside from Princeton, have you been a professor at any other universities?

A. Yes. I began my career at Berkeley and then moved to Caltech, where I became a chair professor. And then in 2006, moved across to Princeton.

Q. What is your educational background?

A. I grew up in Scotland. Went to university at the University of Glasgow, where I got my undergraduate degree. Came across to the States to do my Ph.D., which I did at UC, Irvine. And then went up to Harvard to do a post doc.

Q. What is the focus of your research?

A. The focus of my research is chemical synthesis, which

includes synthetic chemistry, medicinal chemistry, chemical biology, and a little bit of biology.
Q. How many peer-reviewed publications do you have?
A. I looked this up last night; 185.
Q. And what generally do those publications relate to?
A. Same research areas; chemical synthesis, medicinal chemistry, chemical biology.
Q. Have you done any consulting work for the pharmaceutical industry?
A. Yes. Over the last 20 years, I've been working with approximately ten major pharmaceutical companies.
Q. Have you received any honors or awards for your work in the field of chemistry?
A. Recently I won the Nobel prize in chemistry.
Q. And what did you win the Nobel prize for?
A. It was for -- it's called asymmetric organocatalysis.
MS. WIGMORE: If you could turn, please, to Tab 1 of your binder, which is PTX-776.
BY MS. WIGMORE:
Q. Would you please identify that document?
A. Yeah. It's my most recent CV.
Q. Is PTX-776 an accurate summary of your educational and professional experience?
A. Yes.
MS. WIGMORE: Your Honor, Exelixis offers

Professor David MacMillan as an expert in chemistry.

MR. MATHAS: No objection, Your Honor.

THE COURT: You sure you don't want to voir dire him?

MR. MATHAS: No thanks, Your Honor.

THE COURT: All right. You may proceed.

BY MS. WIGMORE:

Q. Dr. MacMillan, could you please turn to JTX-4, which is Tab 2?

A. Yeah.

Q. What patent will you be addressing here today?

A. The '349 patent.

Q. Are you offering an ultimate validity opinion with respect to the '349 patent?

A. No, I'm not.

MS. WIGMORE: If we could please have Claim 3 of the '349 patent.

BY MS. WIGMORE:

Q. Do you recognize Compound IB as the (L)-malate salt of cabozantinib?

A. Yes, I do.

MS. WIGMORE: And if we could highlight the last limitation of Claim 3.

BY MS. WIGMORE:

Q. Is that the limitation that you'll be addressing here

today?
A. Yes, it is.
Q. And the compound referred to in that last limitation, 6,7-dimethoxy-quinoline-4-ol, can we refer to that as the 1-1 impurity?
A. Yes.
Q. Do you understand the parties have agreed that the priority date for the '349 patent is February 10th of 2011?
A. Yes.
Q. Is that the priority date you applied in forming your opinions in this case?
A. I did.
Q. Have you considered the qualifications of a person of ordinary skill in the art for the '349 patent as of that date?
A. Yes, I have.
Q. And have you reviewed both parties' definitions?
A. Yes, I have.
Q. Under both parties' definitions, do you qualify as a person who would be a member of a team a POSA would consult with?
A. Yes.
Q. Would your opinions in this case change depending on whether one party or the others definition were applied?
A. No, they would not.

Q. Now, we'll come to the details of your opinion shortly, but let's first address them at a high level.

Are you responding to certain opinions offered by Dr. Lepore?

A. Yes.

Q. What is your opinion as to whether, as of the priority date, a POSA would have expected the 1-1 impurity to form from the Brown process?

A. As of the priority date, a POSA would not have expected the 1-1 impurity to have formed as a result of the Brown process.

Q. What is your opinion as to whether, as of the priority date, a POSA would have been motivated to control for the 1-1 impurity after completion of the Brown process?

A. Because they would not have expected to have the 1-1 impurity at the end of the Brown process, they would not have been motivated to control for that impurity at the end of the same process.

Q. Now, were you here just now for the testimony of Dr. Khalid Shah?

A. Yes.

Q. And were you here when he testified that Exelixis discovered that the 1-1 impurity was not adequately controlled by the Brown process?

A. Yes, I was. Yes.

Q. With that in mind, what is your opinion as to whether a POSA would have had a reasonable expectation of success in controlling the 1-1 impurity by modifying the Brown process?
A. I don't believe they would have had a reasonable expectation of success or been able to modify the Brown to achieve that required level of impurity.
Q. And we'll dive into those opinions shortly.
But in terms of question of inherency, did you hear Dr. Lepore's opinions on that and Dr. Donovan's opinions?
A. Yes, I did.
Q. Are you responding to those opinions today, Dr. MacMillan?
A. No, I am not.
Q. Do you understand that's being handled by a different Exelixis expert?
A. Yes.
Q. Now, before we get into your opinions, what is an impurity?
A. Impurity is a molecule, a compound, that comes about either during a process where you're performing chemical reactions where a chemical reaction happens on the molecule that's not desirable to generate a molecule that you don't desire, or it can come from a reagent which you're using as part of that process, or it can happen to be an degradation

03:57:39 product, either during a process or after a process.
03:57:41 Q. What is degradation?
03:57:43 A. Degradation is when you have a desired molecule and due to exposure to conditions, whether it's chemicals, whether it's environment, whether it's heat, whether it's light, it will undergo chemical change to, again, become a molecule that you don't necessarily want either, again, during a process or after a process, maybe on storage.
03:58:04 Q. So when you say after a process, can a degradation product form after a compound has been formulated?
03:58:09 A. Yes, it can.
03:58:11 Q. Now, let's start with your first opinion.
03:58:14 Were you here when Dr. Lepore testified that a POSA would have expected the 1-1 impurity to form from the Brown process?
03:58:21 A. Yes, I was.
03:58:22 Q. Do you agree with him?
03:58:23 A. No, I do not.
03:58:26 MS. WIGMORE: If you could please turn to Tab 3 in your binder, which is DTX-291.
03:58:28 BY MS. WIGMORE:
03:58:31 Q. Do you recognize this as the Brown reference Dr. Lepore testified about?
03:58:35 A. Yes, I do.
03:58:37 MS. WIGMORE: If we could please turn to

03:58:38 Scheme 1 in paragraph 99 of Brown, which is on Page 24.
03:58:38 BY MS. WIGMORE:
03:58:47 Q. What is described in Scheme 1 of Brown?
03:58:49 A. Scheme 1 is a synthetic sequence of multiple chemical steps that in combination leads to the production of the (L)-malate salt of cabozantinib.
03:59:00 Q. Do you see the reference to Compound I at the end of Scheme 1?
03:59:04 A. Yes.
03:59:05 Q. What is that?
03:59:05 A. The end of Scheme 1, that is the (L)-malate salt of cabozantinib.
03:59:10 Q. Now, Scheme 1 of Brown, is that part of Example 1?
03:59:14 A. Yes, it is.
03:59:16 Q. And what is described in Examples 1 through 6 of Brown?
03:59:21 A. 1 through 6 of Brown is various processes to generate the (L)-malate salt of cabozantinib.
03:59:27 Q. What, if anything, does Brown disclose about whether the 1-1 compound is a degradation product?
03:59:34 A. It does not disclose that the 1-1 compound is a degradation product.
03:59:38 Q. What, if anything, does Brown disclose about whether the 1-1 compound is a process impurity?
03:59:44 A. It does not disclose it's a process impurity.

Q. Have you heard testimony in the course of this case about genotoxic impurities?
A. Yes, I have.
Q. What, if anything, does Brown disclose about whether the 1-1 compound is genotoxic?
A. The Brown document does not disclose that the 1-1 impurity is genotoxic.
Q. Are you familiar with a term "hydrolysis"?
A. I am.
Q. What is hydrolysis?
A. Hydrolysis, as the name suggests, is basically taking the atoms, the elements of water and adding it to any other compound to either create a new compound that incorporates water or multiple compounds that incorporates the constant the elements of water.
Q. You testified about degradation. Can hydrolysis play a role in degradation?
A. Yes, it can.
Q. Is that a desirable or undesirable result?
A. Most of the time, it's undesirable. There are a few occasions where hydrolysis is desired, but it's when degradation happens, but for the most part, it's undesirable.
MS. WIGMORE: If we could please have PDX-5.
BY MS. WIGMORE:

Q. Dr. MacMillan, in February of 2011, would a POSA, looking at the synthetic scheme, Scheme 1 in Brown, have expected the 1-1 impurity to form through hydrolysis?
A. No, they would not.
Q. And using PDX-5, can you please explain why not?
A. Yes. Would it be okay if I use a laser pointer?
THE COURT: Sure.
THE WITNESS: Okay. Thank you.
So, just to explain this the way I think an organic chemist or a POSA would look at this, if you look at this molecule, you can see there's these two hexagons, which are aromatic rings. And you can see in red these are two chemical rings and the O for oxygen. That's the ether. That's the biaryl ether.
To organic chemists, this is a very, very, very stable compound. It's a stable functional group to the point that they would not expect that that would undergo hydrolysis.
BY MS. WIGMORE:
Q. Dr. MacMillan, the compound shown on this slide is what compound?
A. Oh, I apologize. This compound shown on the slide is cabozantinib, and it's referring to the two red bonds in the red oxygen on the slide.
Q. Now, would the formation of the malate salt make

hydrolysis more likely?

A. No.

Q. What are the reasons for that?

A. Well, so the formation of a malate salt means if -- what would happen is this nitrogen which is shown here will undergo, which is the bottom of the hexagon of cabozantinib, would undergo the proton -- the protonation of the acid would go right there. That would make it more electron deficient. However, you can see on the left-hand side of these two oxygens shown in blue, and these are donating electron density into these ring systems.

What that's doing is effectively deactivating or negating the impact of this proton being on the nitrogen. So, again, the stability of this is such the person of ordinary skill would not expect it to undergo hydrolysis.

Q. Would a POSA have expected that malic acid could catalyze the formation of the 1-1 impurity?

A. No, they would not.

Q. What are the reasons for that?

A. Malic acid is a relatively weak acid in the grand scheme of acids because the proton being here would not sufficiently activate this because of this electron density being added in. As such the person of ordinary skill in the art would not expect that the malic acid to activate this to towards hydrolysis.

Q. And just for the record, the proton you're referring to is the nitrogen at the bottom of the hexagon in the cabozantinib diagram?

A. Yeah, there's three nitrogens in this compound. It's the one lowest on the slide at the bottom of the hexagon. That's the one that would undergo what's called protonation where the hydrogen would associate with it.

Q. So, what did you conclude about whether a POSA would have expected the 1-1 impurity to form by degradation in the Brown process?

A. They would not expect that to happen.

Q. Was the structure that we know today as cabozantinib in clinical development as of the priority date for the '349 patent?

A. Yes, it was.

Q. What was the compound known today as cabozantinib referred to in the published literature before 2010?

A. In the -- excuse me. In the public literature it had that anonymous name. It was known as XL184. That was the name that was given to it for those -- while it was in clinical development.

Q. Was there any definitive connection in the literature between XL184 and cabozantinib at the time of the '349 patent invention?

A. As I said, it was -- XL184 was an anonymous name,

meaning there was no relationship between that name and the structure of what we now know to be cabozantinib.

Q. Before February of 2011, did any of the clinical publications concerning XL184 reveal any concerns about potential impurities or degradation products?

A. No, they did not.

MS. WIGMORE: Now, let's turn to your second opinion. If we could return to the Brown reference, DTX-291, Paragraph 99, again, looking at Scheme 1.

BY MS. WIGMORE:

Q. Where, if at all, does the 1-1 compound appear in this scheme?

A. The 1-1 compound in this scheme is in the top left-hand corner of the scheme. This would be the starting material for this overall process.

Q. Do you recall Dr. Lepore's testimony that a POSA would have monitored and controlled for the 1-1 impurity because it was a starting material in Scheme 1?

A. I do remember that. Yes.

Q. Do you agree with Dr. Lepore?

A. I agree with it, to the extent that it would monitor it for being after the first step. So this is the first chemical reaction, which is the first arrow next to that top left-hand structure. The POSA would be interested in controlling for it at this stage. But beyond that, because

of the number of steps involved, subsequently, it's not a material that you want to be controlling for by the time you got to the end of these numerous steps in that synthetic sequence.

Q. So let's break that down. Still looking at Scheme 1, what product is made by the overall process?

A. The overall process of all these chemical steps ends up at the bottom right-hand corner which is the cabozantinib (L)-malate salt.

Q. If you could look to Paragraphs 101 and 102 of Brown which begin on Page 24 --

A. Mm-hmm.

Q. -- and carry over to 25. What is the first step in this process designated as Step 1.1?

A. This first step is the formation of what's called the 4-chloro-6,7-dimethoxyquinoline.

Q. And from what is that product formed?

A. That product is formed from what we know now refer to as the 1-1 impurity, in that case a starting material.

Q. If you could please turn to the fourth sentence in Paragraph 102 beginning with "The reaction was deemed complete."

Do you see that?

A. Yes.

Q. Could you read that sentence, please?

A. Okay. Hold on.
Q. It's in -- under Section 1.1.
A. I'll let it be blown up.
"The reaction was deemed complete (approximately nine hours) when less than 2 percent of the starting material remained (in process high-performance liquids chromatography HPLC analysis)."
Q. So, again, here we're referring to the first step of the Brown Scheme 1; is that right?
A. Yes.
Q. And what would that sentence have conveyed to a person of ordinary skill in the art?
A. So, to a person of ordinary skill in the art, that means they're only actually halfway through the first step, and yet they're seeing it's still below -- 2 percent of that starting material remains only halfway through the first step.
Q. Reviewing the remainder of Step 1.1, what would that have conveyed to a person of skill in the art?
A. The remainder of this step, the information detailed below is effectively a process to further purify that process, meaning you would expect that the amount of the starting material would be removed to an even larger extent.
Q. So, you have less than 2 percent and then engage in further purification; is that right?

A. That is correct.
Q. And is that all part of the first step of Brown Scheme 1?
A. That is just the first step, yes.
Q. What would a person of skill in the art have expected regarding the amount of the 1-1 impurity if any, that would remain after Step 1.1?
A. They would expect it to be a very small amount of any starting material left at that stage.
Q. Is Step 1.1 the only step disclosed in Example 1?
A. No, it's not.
MS. WIGMORE: If we could please have PDX-6.
BY MS. WIGMORE:
Q. What is shown here?
A. This is all of the steps involved in Scheme 1, and the critical part here is you can see there's multiple chemical steps beyond just this first step.
MS. WIGMORE: Let's have PDX-7.
BY MS. WIGMORE:
Q. What is shown on PDX-7?
A. What I'm showing here is you can see there's Step 1. That's the one we just stalked about, but you can see there's Step 2. And then there's the purification process associated with this. Step 3, same again. Step 4, purification process. Step 5, purification process all the

way before you get to the (L)-malate salt of cabozantinib.
Q. Now, I noticed you haven't marked the bottom left-hand corner with any step. Why is that?
A. So the bottom left-hand corner, these are a branching point. You can see this is a synthetic sequence where you have one sequence. They're called the longest linear sequence. That makes sense because you can see it's the longest number of steps.
You can also see there's this branching point that comes in at this point here which is a shorter number of steps. So I've only focused on the steps which begin from the 1-1 impurity starting material.
Q. So if we're looking at Scheme 1, it's basically the first two rows; is that right?
A. That's correct.
Q. Now, looking at Scheme 1 as a whole, would a person of skill in the art have been motivated to control for the starting material after all those steps were completed?
A. No, they would not.
Q. And what are the reasons they would not?
A. Because as we've already mentioned, there's basically very little of this starting material after Step 1. Now, keep in mind you have all of these other steps and each one of these has a purification component to it. But beyond that, you're also adding reagents which could also react

with it to also remove or purge as we've heard earlier today.

Because of all these purification steps, these purging steps, a person of ordinary skill would not believe there would be any of this material way over here ending up way down here.

Q. And by "way over here," you're referring to Step 1?

A. At the beginning of Step 1, ending up at the end of Step 5.

Q. And so what does that mean as to whether they would be motivated to control for it?

A. Well, if they don't believe that it would be there, they would have no expectation it would be there. There would not be a motivation to control for it.

Q. Now, moving to your next opinion. You were here for Dr. Shah' testimony; is that right?

A. Yes.

Q. And what did he explain about what Exelixis learned about the 1-1 impurity and their development program?

A. They learned --

MR. MATHAS: I object. Dr. Shah just testified, and asking this witness to repeat it is cumulative and irrelevant.

THE COURT: Well, I assume he's going to have some opinion about it or say it somehow -- can you rephrase?

MS. WIGMORE: I can rephrase the question, Your Honor.

MR. MATHAS: Your Honor, I would also like to pose an objection to what I think this line of testimony is going to be about. I think counsel said that this is going to be about reasonable expectation of success.

THE COURT: I didn't -- oh.

MR. MATHAS: And Dr. MacMillan only has two disclosed opinions on reasonable expectation of success, and neither of which responds to the reasonable expectation of success presented by Dr. Lepore which was recrystallization.

MS. WIGMORE: He responded to Dr. Lepore's opinion, and I'll refer the Court, I believe, to Paragraph 11.

MR. MATHAS: I agree he has responded to Dr. Lepore but not on recrystallization.

MS. WIGMORE: Your Honor, he's testifying about reasonable expectation of success. Dr. Lepore gave broad testimony about what a person of skill would have been motivated to do and whether they would expect success. Dr. MacMillan is responding to those opinions. And he disclosed that he would do so, among other places, in paragraph 11 of his expert report.

THE COURT: All right. Well, I'm going to allow it, so go ahead.

BY MS. WIGMORE:

Q. Now, were you here when Dr. Shah testified that Exelixis discovered an impurity after the Brown process was completed?

A. Yes.

Q. And were you here when Dr. Lepore testified a person of skill in the art would have added a recrystallization step to the Brown process?

A. Yes.

Q. In terms of the '349 patent, did Exelixis achieve the claimed purity level for the 1-1 compound by adding a recrystallization step to the Brown process?

A. No.

Q. At a high level, what did they do instead?

A. At a high level, they introduced multiple changes, including changing the substrates, changing reagents, changing the number of steps, changing the solvents, changing purification methods.

They came up with a very different process able to effectively achieve the removal of the 1-1 impurity.

Q. Dr. MacMillan, if you could please turn to Tab 4 in your binder, which is PTX-36.

What is this document?

A. This is the manufacturing process development document from Exelixis.

Q. And if you could just page through Figures 7 through 10 on Pages 7 through 13 of this document, and explain generally what is shown in those figures.
A. So, 7 through 10 is basically beginning with the process route that the medicinal chemists started with -- those are the chemists who are in the lab, discovered the molecule on a very small scale. And from that process, is the evolution from that all the way through to what became eventually the commercialized manufacturing of cabozantinib (L)-malate salt.
MS. WIGMORE: Please turn to Figure 8 on Page 9 of this exhibit, PTX-36.
BY MS. WIGMORE:
Q. What is shown in Figure 8?
A. Figure 8 is what's known as the A-2 process.
Q. And do you understand that the A-2 process is the process disclosed in Brown?
A. Yes. I have heard this referred to a number of times in the case as A-2 is equal to the Brown process.
Q. And what is the B-2 process?
A. The B-2 process is what is now the commercialized process, the process of the '349 patent.
Q. Have you analyzed the differences between the A-2 process and the B-2 process?
A. Yes, I have.

Q. Now, focusing on Figure 8, which is process A-2, can you please walk us through the differences between the A-2 process from Brown and the B-2 process from the '349 patent?

A. Sure. So, if you focus on the very top series of chemical reactions, if you look at the molecule in the middle called 184-1-2. And you'll notice to the right of it is an arrow. That arrow means chemical reaction.

If you look above the arrow, there's this hexagon with an NO_2, that's a nitro group. Those are the kind of groups you would find on, like, explosives like TNT and things like that.

Now, when you go to the B-2 process from the A-2, they don't use this molecule. They actually get rid of this nitro. This now becomes what's called an amino. That's a significant difference, a big difference.

If you go below that same arrow, it says DMAP 26, that's the base. This is a relatively mild base.

When you move to the B-2 process, this now becomes sodium pentoxide. Pentoxide is a relative aggressive, very strong base. So, two very large differences.

Now, as a result of this change, this product you generate, 184-1-3 is a completely different molecule that doesn't even show up in the B-2 process. Because it's got this nitrogen group here. Because it's a completely

different molecule, they have to use a completely different chemical step over here. This is on the left-hand side the arrow with PD/C, that's palladium. They have to employ this step to remove that nitro to make into what's called a NH_2. When you Form 184-1-4.

So that's going to have its own set of impurities associated with it again. And then beyond that, if you go to the very last step, you can see the last step on the right-hand side, there's -- down this vertical arrow. To the right of it, it says EtOH, that's ethanol, and water, H2O.

They remove this and use a completely different solvent in that part of the process as well. There's a number of other changes they make along the way. I would argue some of the most significant ones.

Q. How does the number of steps in the B-2 process compare to the number of steps in the A-2 process.

A. The B-2 process is shorter. It's one step shorter than the A-2 process.

Q. But is it fair to say they're different steps?

A. Oh, yeah. I mean, it's -- if you've got a different number of steps, it means you have to have different chemistries involved and you have to have different molecules involved, which you can plainly see, for example, 184-1-3.

04:17:25 Q. Do you agree with Dr. Lepore that a person of skill in the art would have had a reasonable expectation of success in achieving the claimed purity level of Claim 3 by adding a recrystallization step to the Brown process?
04:17:38 A. No, I do not.
04:17:40 Q. Why not?
04:17:40 A. Because if it was that simple, I don't think Exelixis would have went to all of these -- extent of effort to be able to solve this problem for all these many different changes if it just involved introducing a simple recrystallization step.
04:17:54 Q. Were there purification steps in the existing Brown process?
04:17:57 A. Yes, there were.
04:17:58 Q. Would there have been reason to believe that adding another purification step in the form of recrystallization would lead to a different outcome?
04:18:05 A. No, there would not.
04:18:08 Q. Would a person of skill in the art have had a reasonable expectation of success in achieving a claimed purity level by making any other changes to the Brown process, including the ones that you just walked us through?
04:18:21 A. Not with any reasonable expectation of success, no.
04:18:25 MS. WIGMORE: Thank you, Dr. MacMillan.
04:18:26 I would like to move in PTX-776 and PTX-36.

04:18:34 MR. MATHAS: No objections, Your Honor.
04:18:34 THE COURT: All right. Admitted without
04:18:36 objection.
04:18:36 (PTX Exhibit Nos. 776 and 36 were admitted into
04:18:43 evidence.)
04:18:43 MR. MATHAS: Your Honor, may I hand up a small
04:18:45 cross binder?
04:18:46 THE COURT: Sure.
04:20:07 MR. MATHAS: Your Honor, I think I'm going to do
04:20:09 it without a binder.
04:20:10 THE COURT: Well, it's all right if you -- I
04:20:13 mean, your choice.
04:20:14 MR. MATHAS: I think the only thing would be the
04:20:16 report of the deposition, maybe something else that we could
04:20:18 look at. So I think we can proceed, if it's all right.
04:20:20 THE COURT: All right then. Go ahead then.
04:20:22 CROSS-EXAMINATION
04:20:22 BY MR. MATHAS:
04:20:23 Q. Good afternoon, Dr. MacMillan.
04:20:23 A. Good afternoon, Mr. Mathas.
04:20:26 Q. Real quick, on this point about hydrolysis, just so
04:20:30 I'm clear, hydrolysis is when a compound reacts with water;
04:20:34 is that right?
04:20:34 A. Yes.
04:20:35 Q. Okay. Now, you agree that the 1-1 is -- the 1-1

compound is the starting material that is used in the Brown Example 1 process; right?

A. Yes.

Q. And you agree that it is possible for a starting material to carry through a synthesis into the final step; is that right?

A. Oh, sure, yeah, it's possible.

Q. Okay. And you said during your direct that you didn't believe -- and let's just take one brief moment and we'll give you a binder.

All right. Dr. MacMillan, so on your direct, you said that in your opinion, you didn't believe that the 1-1 would carry through in the Brown process because there were five intermediate steps; is that right?

A. Yeah. I mean, it's always possible a starting material can get to the end of a sequence, that's why I mentioned at the end of Step 1. But for that overall process, because of all the purification and also chemical reactions, I thought it would be -- it would be unlikely.

Q. Okay. So simpler question than that, though, and it would be unlikely because it would have to go through 5 intermediate steps; right?

A. It's more -- it's not the number of steps, it's the number of purification steps and other reagents that would be exposed to.

Q. And -- but when you put your slide up, you showed us five steps that you said it would go; through right?
A. I did, sure, yes.
Q. Okay. Now, previously, you opined that the synthetic route in Brown disclosed seven intermediate steps; right?
A. It does, yes.
Q. All right. Now, two of those steps are side steps; right?
A. Yeah, those are the ones I was talking about, you know, the branching point, coming in from the left-hand side.
Q. Those are side steps; right?
A. Yes.
Q. Okay. And -- and for purposes of your testimony here, five intermediate steps is the reason why we wouldn't expect the 1-1 to carry through from the starting material into the final product; true?
A. It's not the number of steps, it's the details of those steps. It's because it's the purifications and the reagents. You could find five chemical steps that wouldn't do anything. But it's not the number, it's the details of what's under each of those chemical steps.
Q. Okay. Now, Brown, as we looked at -- as you looked at on direct, allows there to be 2 percent of the starting material I think you said halfway through Step 1; is that

right?
A. That's correct.
Q. And now, 2 percent, that's 20,000 PPMs mathematically; right?
A. That's correct.
Q. Okay. And so that's halfway through Brown Step 1. And then at that point, it's true, isn't it, that additional amounts of the 1-1 would be further removed by the crystallization that occurs at the end of Step 1?
A. Based on the details of the fact that was presented in that description, that would be the expectation.
Q. Right. The POSA would reasonably expect that crystallization at the end of Step 1 would further reduce the 1-1 impurity level; right?
A. Because of the nature of the expect -- of the crystallization shown, not just any crystallization, that specific crystallization.
Q. And I get that, but in the context of the Brown process, Step 1, it's your opinion that the crystallization at Step 1 would further reduce the 1-1 impurity level; right?
A. Yes.
Q. And then, as I understand your opinion, you suggest that remaining 1-1 impurity would be purged into subsequent Steps 2 through 5; right?

A. Correct.
Q. Okay. Now, you're not giving the opinion that there would be 0 PPM of the 1-1 left at the end of the process; right?
A. Just below detectable levels.
Q. Okay. And so that is some non 0 amount of the 1-1 impurity; right?
A. Yeah, it's not to waste the Court's time, but it's one of those things, once it's below detectable, you can never see an absolute 0, it's impossible.
Q. Okay. Now, and -- but even though it is a non-zero amount of the 1-1, it's your opinion that the POSA would have no motivation to monitor for it; right?
A. If the POSA believes that it's not there, there's no reason to monitor to for it.
Q. Now, in reaching your opinions on motivation, Dr. Lepore, you do not consider any FDA or other regulatory guidance -- I called you Dr. Lepore. I apologize.
In reaching your opinions, Dr. MacMillan, you did not consider any FDA or other regulatory guidance documents on controlling impurities; right?
A. Well, no because if the person of ordinary skill does not believe that the molecule is going to be there, then, yeah, that would -- you don't need to sort of worry about that -- those guidelines for that component of it.

Q. Okay. So you -- just to make sure the answer is clear: You did not, for example, consider the FDA's guidance on controlling genotoxic impurities; correct?
A. Correct.
Q. Okay. And, in fact, you didn't even consider whether or not the 1-1 impurity was potentially genotoxic; right?
A. I mean I've subsequentially learned it is genotoxic, but I don't believe a POSA looking at it would have any notion that it would be genotoxic.
Q. As of the time that we took your deposition, you didn't know whether or not the 1-1 impurity was genotoxic; right?
A. That is correct. I think I said I didn't -- I couldn't remember.
Q. Okay. And so in forming -- in forming your opinions prior to that, you didn't have an understanding that the 1-1 was genotoxic; right?
A. I couldn't remember, yes.
Q. Okay.
A. That's correct.
Q. And so, therefore, you didn't consider whether or not a POSA would treat genotoxic impurities differently than they would treat other impurities; correct?
A. Yeah, I don't think -- at that stage that's not something I thought about, whether we treat them differently

04:26:23 or not because, quite frankly, there was nothing in the -- the Brown document that suggested it would be genotoxic. A person of ordinary skill in the art would not be thinking about that.

04:26:31 Q. Simpler question, Dr. MacMillan: You didn't consider whether a POSA would treat genotoxic impurities differently than other impurities; true?

04:26:40 A. That is correct, yeah.

04:26:41 MR. MATHAS: No further questions, Your Honor.

04:26:43 THE COURT: All right. Any redirect?

04:26:44 MS. WIGMORE: No, Your Honor.

04:26:46 THE COURT: All right. Dr. MacMillan, thank you. You're -- watch your step stepping down.

04:26:55 MS. PIROZZOLO: Plaintiffs call Dr. Allan Myerson.

04:27:28 DEPUTY CLERK: Please state and spell your full name for the record.

04:27:33 THE WITNESS: Yes. Allan, A-L-L-A-N. Stuart, S-T-U-A-R-T. Myerson, M-Y-E-R-S-O-N.

04:27:38 ALLAN MYERSON, the witness herein, after having been duly affirmed under oath, was examined and testified as follows:

04:27:38 THE WITNESS: I do.

04:27:57 DIRECT EXAMINATION

04:27:57 BY MS. PIROZZOLO:

Q. Could you please introduce yourself to the Court?
A. Yes. My name is Allan Myerson.
Q. Have you been retained by the Plaintiff as an expert witness in this case?
A. I have.
Q. Generally, what issues have you been asked to address?
A. I've been asked to respond to the opinions of Dr. Donovan and Lepore on the validity of the '349 patent.
Q. Are you being compensated for the time you're spending on working on this case?
A. I am.
Q. Does your compensation depend on the substance of your opinions or the outcome of the case?
A. It does not.
Q. Have you prepared some slides for your discussion today?
A. I have.
MS. PIROZZOLO: Okay. Let's call up Plaintiff's Demonstrative Exhibit 4.
BY MS. PIROZZOLO:
Q. Dr. Myerson, where do you work?
A. I work at the Massachusetts Institute of Technology in Cambridge, Massachusetts.
Q. What do you do at MIT?

04:29:04 A. I'm a professor of chemical engineering.
04:29:06 Q. How long have you been a professor of chemical engineering?
04:29:09 A. It will be 47 years in January.
04:29:13 Q. What are your responsibilities at MIT?
04:29:16 A. Research and teaching.
04:29:18 Q. What courses do you teach?
04:29:19 A. I teach an elective course in pharmaceutical engineering to seniors and graduate students, and a graduate course in crystallization science and technology to graduate students.
04:29:32 Q. Do you perform research?
04:29:34 A. I do.
04:29:36 Q. What is the primary focus of your academic research?
04:29:40 A. My primary focus is pharmaceutical manufacturing with an emphasis on continuous pharmaceutical manufacturing, separation and purification processes, particularly crystallization-related problems. Also, the development of novel pharmaceutical dosage forms.
04:29:59 Q. Have you published any scientific papers?
04:30:02 A. Yes. Approximately 290 refereed papers.
04:30:07 Q. What do those publications generally relate to?
04:30:09 A. Basically the same subjects that I just described in my research; pharmaceutical manufacturing, separation processes, particularly crystallization, pharmaceutical

04:30:22 formulations and fundamental studies of crystallization mechanisms.

04:30:28 Q. Could you briefly describe your experience with pharmaceutical formulations?

04:30:32 A. Yes. A few examples. I helped develop a formulation of aliskiren hemifumarate, which is a Novartis drug during our work on the -- work with the Novartis-MIT Center for Continuous Manufacturing.

04:30:51 Another project that myself and some colleagues had at MIT was called Pharmacy on Demand, where we developed refrigerator-size units that could synthesize, purify, and formulate 15 different generic drugs. And I was responsible for the purification and the formulation of all 15 different drugs.

04:31:11 And just recently, I've been working on a project with Takeda Pharmaceuticals in developing a new formulation of one of their existing drugs, which is a polyclonal antibody.

04:31:24 MS. PIROZZOLO: Could you turn to Tab 1 in your binder, which is Plaintiff's Exhibit 773.

04:31:26 BY MS. PIROZZOLO:

04:31:31 Q. Is this a copy of your CV?

04:31:32 A. Yes.

04:31:34 Q. Does it have an accurate summary of your educational and professional experience?

A. It does.

MS. PIROZZOLO: Your Honor, Plaintiff offers Dr. Myerson as an expert in the subject of separation and purification methods, crystallization, pharmaceutical formulation, and pharmaceutical manufacturing.

MR. LOMBARDI: No objection, Your Honor.

THE COURT: All right. You may proceed.

MS. PIROZZOLO: Let's turn to the '349 patent, which is Tab 2 in your binder. And let's go to Column 3, Line 29.

BY MS. PIROZZOLO:

Q. There's a paragraph beginning with the word "accordingly."

What is your understanding, based on this paragraph, of the need the '349 patent is directed to?

A. Well, it's indicating it's directed to developing pharmaceutical compositions such that they are essentially free process byproducts and they're talking about pharmaceutical compositions of Compound AI, which is cabozantinib.

MS. PIROZZOLO: Let's go to Column 22, at Lines 8 through 27.

BY MS. PIROZZOLO:

Q. What does the patent teach about the 1-1 impurity that we've been talking about?

A. This part of the patent first shows the structure of the -- the impurity that we're talking about, the 1-1 impurity, and indicates it needs to be minimized.

Q. Does the '349 patent teach a skilled artisan how to minimize the 1-1 impurity?

A. It does.

Q. What does the '349 patent teach in that regard?

A. It teaches a synthetic process, which results in a very low level of the 1-1 impurity.

MS. PIROZZOLO: Now, let's go to Claim 3 of the patent.

BY MS. PIROZZOLO:

Q. In general, what is Claim 3 of the '349 patent directed to?

A. Well, first, it's developed to a pharmaceutical composition for oral administration of Compound IB, Compound IB being cabozantinib (L)-malate, and that pharmaceutical composition needs to be essentially free of the 1-1 impurity, it has to contain one or more of four different classes of excipients, and it needs to be a tablet or a capsule.

Q. And what does the patent say with regard to the term "essentially free"?

A. The patent defines essentially free as being less than 200 parts per million of the 1-1 impurity.

Q. And can you explain what parts per million means?

A. Yes. A parts per million means one part in a million parts by weight. So, to give it a simple example something that has a 1 percent -- 1 percent of something has 10,000 parts per million. A tenth of a percent is a thousand parts per million. So 200 parts per million is 0.02 percent.

Q. Now, in terms of Claim 3, what must be essentially free of the impurity?

A. The pharmaceutical composition.

MS. PIROZZOLO: Okay. Let's turn to Slide 3.

BY MS. PIROZZOLO:

Q. Is the invention described in Claim 3 of the '349 patent embodied in any Exelixis products?

A. Yes. In the two Exelixis products Cabometyx, which is the tablets, and Cometriq, which are the capsules.

Q. In your opinion, did the invention of the '349 patent offer benefits?

A. Yes. It was necessary, as we've heard from various witnesses, to control the 1-1 impurity because it turns out it was genotoxic to lower levels, and control of the impurities in the drug product is very important, both on the manufactured drug product and on stability so it has a shelf life.

Q. Now, you mentioned you're responding to Drs. Lepore and Donovan.

MS. PIROZZOLO: Turning to Slide 4.

BY MS. PIROZZOLO:

Q. Could you briefly summarize your response?

A. Yeah. First, there's no motivation to control for the 1-1 impurity since the prior art didn't teach that it was an impurity that needed to be avoided in a pharmaceutical composition.

There was no reasonable expectation of success in controlling the impurity giving any lack of teaching in how the -- in the prior art and how the impurity formed, and that the Brown method would not necessarily produce API essentially free of the 1-1 impurity. And much less, it would not lead a skilled artisan to create a pharmaceutical composition essentially free of the 1-1 impurity.

MS. PIROZZOLO: Now, let's turn to Slide 5.

BY MS. PIROZZOLO:

Q. Can you explain how impurities can arise in a pharmaceutical composition?

A. Yes. We have four places that impurities can -- can arise. First, in the synthesis of the API, that is making the API, and that can include process impurities and byproducts.

Secondly, when we blend the API with excipients, the API can react with excipients to form impurities.

Third, when we manufacture the drug product,

particularly making a tablet, the -- the drug product or the -- the formulated drug product undergoes a process where it sees pressure, heat, humidity, various physical stress, and that can cause impurities.

And, of course, the impurities can form during the shelf life because of degradation of the API.

Q. Now, let's focus on the active pharmaceutical ingredient, and Dr. MacMillan touched on this, but what kind of impurities can form in the API?

A. Yeah. There are -- there are three general -- three general classes. We can have unreactive reactants or solvents, we can have process intermediates or side products, and we can have degradation impurities.

Q. Okay. How can carry through of starting intermediate reactants cause impurities?

A. Right. So -- so, again, if we look at a very simple process that we have, a multi-step process, and in each step we are doing the chemical reaction and that chemical reaction involves reagents and solvents, and hopefully we're making what we want to make. But not all of our components will react and we'll get some components that go into side reactions, and we might get some degradation products.

Now, typically, we would do what are called work up steps or purification steps between each stage so that in the next stage we have something that's at least fairly pure

of what we're trying to make and we carry that through to the next stage going on to the final product.

Q. How can byproducts and process impurities form?

A. Byproducts form when we have chemical reactions that occur which are not the chemical reactions we want to occur. So, that's -- that's what I would call a byproduct.

Q. And how do degradation products form?

A. When something that we tried to form reacts to breakdown to something else.

Q. Can steps be taken to eliminate or minimize these types of impurities in synthesis of an API?

A. Yes. Well, typically, we have what are called work up steps or purification steps between each stage; these include things like solvent extraction, distillations, crystallization, among others.

Q. Are these steps always effective?

A. No.

Q. Now, you mentioned that impurities can also arrive during formulation of the pharmaceutical composition.

A. Yes.

Q. Could you explain how that may occur?

A. Yes. So, we have -- we have the blending with excipients. And as we've seen previously in other testimony, the API can react with excipients forming degradation products.

Q. Now, going back to the invention in the '349 patent, did you review information about Exelixis' work to develop that invention?
A. I did.
Q. Could you briefly summarize the types of materials you reviewed?
A. Yes. I reviewed the Exelixis NDA, other Exelixis development documents that weren't in the NDA, some lab notebooks at various times, as well as other background material that was produced in the case.
MS. PIROZZOLO: Could you turn to Tab 4, which is Plaintiff's Exhibit 35?
THE WITNESS: Yes.
BY MS. PIROZZOLO:
Q. What is Plaintiff's Exhibit 35?
A. This is an excerpt from Exelixis NDA called the "manufacturing process development of cabozantinib (S)-malate," and -- and it was part of the FDA submission.
MS. PIROZZOLO: Now, could you turn to Figure 7 on Page 7 of Plaintiff's Exhibit 35.
THE WITNESS: Yes.
BY MS. PIROZZOLO:
Q. What is shown in Figure 7?
A. Figure 7 is a process that was called Process A-1, and it was one of the small scale -- early small scale

processes used by Exelixis to produce cabozantinib (L)-malate.

Q. Did Exelixis discover any problems with the A-1 process?

A. They did.

Q. What were the problems?

A. Well, one of the biggest problems they discovered was if we look at the synthesis group, we start with 1-1 and we react that to form 1-2. And then we react 1-2, to form the next one in the sequence, 1-3. But, unfortunately, the 1-3 was decomposing to form 1-1. And, in fact, 20 percent of the 1-3 was decomposing to 1-1, which is the first discussion in paragraph 6.4.2.1.1.

Q. Did Exelixis attempt to control for the formation of 1-1 in the A-1 process?

A. They did a couple of things. They did what's called a re-slurry of the 1-3 to try to purge the 1 -1, and -- which was not wildly successful. They also did some other things related to problems with other steps in the process.

Q. Okay. Did they add a reagent at the intermediate step?

A. Yes.

Q. Were the modifications successful at controlling the 1-1 impurity?

A. No.

MS. PIROZZOLO: Okay. Could you turn to Page 8 of Plaintiff's Exhibit 35.

THE WITNESS: Yes.

BY MS. PIROZZOLO:

Q. Did Exelixis encounter problems other than the formation of the 1-1 impurity with the A-2 process?

A. Yes. Well, the A-2 process, they first still were having trouble with the 1-2 to 1-3 conversion, and they were still seeing 1-1 there. But they also found that the use of ethanol in the final salt forming step was producing ethanol esters of malic acid in the product stream which were difficult to detect and remove.

Q. Did Exelixis modify the A-2 process in an attempt to minimize the 1-1 impurity?

A. They did.

Q. What did Exelixis do?

A. Well, they -- they -- as we heard from Dr. MacMillan, they actually changed the chemistry. So, what they did was they eliminated the step from 1-2 to 1-3 and they changed the chemistry to go directly from 1-2 to 1-4, thus eliminating the 1-3 that was decomposing to form 1-1.

Q. Did these changes control formation of the 1-1 impurity?

A. They did.

Q. Did Exelixis further -- did Exelixis modify the B-1

process?
A. They did. They modified the conditions used in the final salt formation step by adding a vacuum distillation to reduce the heat and water required such that they would do things at a -- at a lower temperature with less water. Again, that helped minimize 1-1.
Q. Okay. Were these modifications enough to control for the formation of 1-1?
A. Yes. The B-2 process was very effective in controlling for 1-1.
Q. Okay. Now, looking at Plaintiff's Exhibit 35, are the process modifications that we just discussed described in Exhibit 35?
A. Yes.
MS. PIROZZOLO: Could you turn to Table 2 on Page 16 of Exhibit 35?
THE WITNESS: Yes.
BY MS. PIROZZOLO:
Q. What does Table 2 show?
A. Table 2 is a table that shows, first, lists on the left the four processes A-1, A-2, B-1 and B-2. And it looks at the contents of the 1-1 impurity made in each of these processes and we see in the A-2 process, it ranges from 35 to 411 PPM. In the B-1 process, 84 PPM. And in the B-2 process, less than 2 to 12 PPM. In addition, the yields in

04:47:03 the B-2 process and the overall purity in the B-2 process were very good.

04:47:09 Q. What is the process used for the commercial manufacturer of Cabometyx and Cometriq?

04:47:15 A. It is the B-2 process.

04:47:18 MS. PIROZZOLO: Okay. Now, could you turn to Tab 5 in your binder, which is Plaintiff's Exhibit 47?

04:47:21 BY MS. PIROZZOLO:

04:47:27 Q. What is Exhibit 47?

04:47:29 A. Exhibit 47 is from the NDA for the cabozantinib tablets and it talks about the drug product development.

04:47:43 MS. PIROZZOLO: Please turn to Page 18 of Plaintiff's Exhibit 47. And turn to Table 4.

04:47:46 BY MS. PIROZZOLO:

04:47:53 Q. What is depicted in Table 4?

04:47:55 A. Yes. Table 4 is an excipient compatibility study particularly aimed at looking at the two genotoxic impurities that had been identified, 1-1 and 1-4, and how they would occur -- increase over time when the API was mixed with various excipients and various combinations at both a wet condition at 40 degrees C and a dry condition at 40 degrees C.

04:48:31 Q. What does Table 4 show about the formation of the 1-1 impurity with different excipients?

04:48:38 A. Yes. Well, if we compare the amount of the 1-1

impurity, for example, in any column compared to the amount that was in the A -- that's in the API at that time, we see that any mixture of the API and excipients generally resulted in an increase in the amount of 1-1 impurity. Thus, 1-1 impurity was forming at a higher rate when excipients were in contact with the API than the API itself.

Q. Was this information relevant to making a pharmaceutical composition of cabozantinib (L)-malate that was essentially free of the 1-1 impurity?

A. Yes. What it tells you is you want to start with a very low level of the 1-1 impurity to ensure that the formulated drug product remains essentially free, both when manufactured and on the shelf.

Q. Were there any concerns at Exelixis about formation of the 1-1 impurity occurring during manufacturing of tablets or capsules?

A. Yes.

Q. What were those concerns?

A. Again, we have interaction with excipients and then we also have interaction with water, heat, and physical stress or -- or force.

Q. Now, we've talked about the B-2 process. Is that the process disclosed in the '349 patent?

A. Yes.

Q. Did the development of the B-2 process for

synthesizing cabozantinib (L)-malate contribute to minimizing the formation of the 1-1 impurity in pharmaceutical compositions?

A. Yes. It was the key feature of the '349 patent because it teaches a POSA how to make cabozantinib (L)-malate with exceptionally low levels of the 1-1 impurity.

MS. PIROZZOLO: Okay. Now, let's take a look at the '349 patent again, which is joint Exhibit 4, at Columns 5 through 7.

BY MS. PIROZZOLO:

Q. What is shown in Columns 5 through 7 of the patent?

A. Column 5 through 7 show six examples of pharmaceutical formulations, including that of a tablet and a capsule.

Q. Okay. Before Exelixis' work was it known that 1-1 was a degradation impurity?

A. It was not.

Q. What is a genotoxic impurity?

A. A genotoxic impurity is an impurity that reacts or impacts your DNA or a person's DNA.

Q. Can a skilled artisan tell without testing whether an impurity is genotoxic?

A. No. A test, generally -- generally the Ames test is required.

Q. At some point, did Exelixis discover that the 1-1 impurity was genotoxic?
A. Yes. It was in the period they were developing the B processes that they -- that they discovered that the 1-1 impurity was genotoxic.
Q. Now, you mentioned the Ames test. Could you describe how Exelixis discovered that the 1-1 impurity was genotoxic?
A. Yes. So, when they were in the period of developing the B processes, they looked at potential structures that were genotoxic and performed the Ames test on them. I think they did the Ames test on four compounds.
Q. Okay. Please look at --
MS. PIROZZOLO: Let's pull up Slide 9 of your presentation.
BY MS. PIROZZOLO:
Q. What is shown on Slide 9?
A. Slide 9 are the four compounds that -- that were tested for genotoxicity by the Ames test.
Q. Okay. And what did -- what does this testing show about these four compounds that were tested?
A. Well, what -- what I think is very interesting is if we look at the -- the first one on the left, which is Ames positive, that's the 1-1 impurity. But if we wanted to look at the one right next to it, which is Ames negative, the only difference between the two is a chlorine in place of

the OH group. And that's Ames negative.

It shows that you cannot just look at structures and know if they're going to be Ames positive or Ames negative, you have to do the test.

Q. Before Exelixis identified the 1-1 impurity as a genotoxin, was that fact publicly known?

A. No.

MS. PIROZZOLO: Now, let's turn to Slide 10.

BY MS. PIROZZOLO:

Q. We've talked walked through some of your -- some of Exelixis' work. Could you summarize, in your opinion, the key findings made by Exelixis about the 1-1 impurity?

A. Well, the first is very important, that they found that 1-1 could form as a degradation product during the synthesis of the API. They also found that 1-1 could form when the cabozantinib (L)-malate was exposed to heat and water.

Also, that it could form when cabozantinib (L)-malate was exposed to certain excipients.

And, of course, as we know --

MR. LOMBARDI: I thought --

MS. PIROZZOLO: This is a mistake.

MR. LOMBARDI: I thought it might have been. I just wanted to check.

MS. PIROZZOLO: Yeah, yeah. I apologize. We

04:54:37 had a replacement slide.

04:54:39 Here.

04:54:39 THE COURT: Oh, okay.

04:54:40 MS. PIROZZOLO: Can we get the --

04:54:48 BY MS. PIROZZOLO:

04:54:49 Q. And the last bullet point, Dr. Myerson?

04:54:51 A. The 1-1 impurity is genotoxic, which we just discussed.

04:54:56 MS. PIROZZOLO: Okay. Now, could you turn to Tab 9 in your binder, which is a abbreviated version of Joint Exhibit 8.

04:55:08 BY MS. PIROZZOLO:

04:55:10 Q. Is this a portion of the file history of the '349 patent?

04:55:16 A. Yes.

04:55:18 Q. Did you consider -- did you review the prosecution history of the '349 patent in rendering your opinions?

04:55:25 A. Yes.

04:55:28 Q. Now, I'd like to turn to your opinions on validity. And in your response to Drs. Donovan and Lepore, what are your key disagreements with Drs. Donovan and Lepore?

04:55:47 A. Well, first, I don't agree that the Brown reference, which is what we've heard a lot about which is the A-2 process, will always produce cabozantinib (L)-malate that's essentially free of the 1-1 impurity.

I also think there's a significant gap in the opinions of Dr. Lepore and Dr. Donovan. From Dr. Lepore, we heard about the API. From Dr. Donovan we heard about the formulation and the final drug product. But no one really discussed how -- what the 1-1 impurity could form during the manufacturing of the drug product and on the shelf. Thus, I don't -- I don't think that that gap has been closed.

In addition, it's clear that a key feature of the invention was the ability to formulate -- ability to manufacture API, as described in the '349 process, that was very, very low in the 1-1 impurity. And, thus, can be formulated into a drug product that could be reliably manufactured and be essentially free of the 1-1 impurity.

Q. Now, turning to Slide 11. What did you consider in forming your response to Drs. Donovan and Lepore?

A. Well, first, I looked at the scope and contents of the prior art, the differences between the prior art and the claimed invention, whether there was any motivation to modify Brown. And whether there was a reasonable expectation of success in reaching the claimed invention. And then objective indicia of non-obviousness.

MS. WIGMORE: Now, turning back to the patent, Joint Exhibit 4.

BY MS. WIGMORE:

Q. What is the priority date of the '349 patent?

A. Yes, it's February 10th, 2011.
Q. Now, your definition of a skilled artisan is on Slide 12; correct?
A. Yes.
Q. Did you apply this definition in forming your opinions in this case?
A. I did.
Q. Are you familiar with Dr. Donovan's definition of a skilled artisan?
A. I am.
Q. Would your opinions change under Dr. Donovan's definition?
A. It would not.
Q. As of February 2011, did you meet the definition of a skilled artisan under both parties' definitions?
A. Yes.
Q. Now, Drs. Donovan and Lepore, if we look at Slide 12 -- or 13, mention several references in rendering their -- their obviousness opinions --
THE COURT: Ms. Pirozzolo, I think maybe this is the appropriate place to stop for the day.
MS. PIROZZOLO: Okay.
THE COURT: Before you start getting into new things. So, we'll -- so that's it for today.
Dr. Myerson, you can step down. Watch your

04:59:37 step.

04:59:37 Just looking ahead to tomorrow, Plaintiff,

04:59:47 you're still expecting to call Dr. Trout, Dr. George, and

04:59:51 Mr. Tate?

04:59:51 MS. PIROZZOLO: And, also, Dr. Koleng.

04:59:53 THE COURT: Oh, okay. All right.

04:59:58 All right. Well, we'll be in recess until

05:00:00 tomorrow.

05:00:01 MS. PIROZZOLO: Thank you, Your Honor.

05:00:02 DEPUTY CLERK: All rise.

(Court was recessed at 5:00 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Heather M. Triozzi
Certified Merit and Real-Time Reporter
U.S. District Court